Orygen
The National Centre of Excellence in Youth Mental Health

Clinical practice in early psychosis

Managing incomplete recovery during first episode psychosis

Introduction

While the vast majority of young people who develop a first episode of psychosis respond well to initial treatment and have a remission of their symptoms, some young people will continue to experience symptoms and thus show signs of early treatment resistance. Because early treatment response is thought to be one of the strongest predictors of subsequent outcome,[1,2] preventing enduring symptoms of psychosis and associated impaired social functioning should be the primary aim of treatment for first episode psychosis (FEP).

Prolonged recovery during the early phases of psychotic illness may have important biological and psychosocial consequences, such as: ongoing disruption to social, interpersonal and vocational functioning; demoralisation due to the experience of powerlessness, fear, isolation; and development of continued treatment resistance. Thus concerted effort is required to address incomplete recovery from psychosis early. These will consider the contribution of illness-, person- and treatment-related factors to the observed poor response to treatment, and suggest treatment modifications to achieve recovery as soon as possible.

This clinical practice point is designed to help clinicians understand:

- why it is important to address incomplete recovery
- the principles for effective treatment
- how to use evidence-based pharmacological and psychological strategies to address incomplete recovery in everyday clinical practice.

> “As clinicians, you always want to minimise the distress of psychotic symptoms [for young people] ... this means actively managing incomplete recovery.
>
> Senior Clinician
> EPPIC, Orygen Youth Health Clinical Program

What is incomplete recovery?

Failure to respond to treatment for psychosis has been traditionally referred to as ‘treatment resistance’. Research in this field has been hampered by a lack of consistent definitions of the concept and validated assessment instruments. The term ‘treatment resistance’ has been used particularly to describe failure of positive psychotic symptoms to remit following pharmacological treatment with antipsychotic medication. This narrow focus on positive symptoms has stemmed from the traditionally poor recognition of other symptoms that affect outcome in psychosis

(e.g. cognitive symptoms) or the belief that certain symptom domains were unresponsive to medication (e.g. negative symptoms). Hence treatment response has been, in the past, largely evaluated on the basis of effect on positive symptoms, which is a limited view that ignores important outcome dimensions like social and vocational functioning.[3]

However, as treatment outcome goals in psychosis research have broadened to include functional recovery and quality of life, the definition of treatment response and resistance have been reviewed and modified, and the term 'incomplete recovery' was deemed more appropriate.

> 'Clinically, the broader notion of 'incomplete recovery' may be useful, as it acknowledges the presence of disability in functional and psychosocial aspects that is persistent despite adequate treatment, referring to psychotherapeutic and psychosocial interventions as well as antipsychotic medication. Further, unlike the rather negative label of 'treatment resistance', the term 'incomplete recovery' also recognises the potential for a better therapeutic outcome.'[4]

It is important to note that there are two types of incomplete recovery:

1. Treatment resistance, which refers to situations where people are receiving appropriate evidence-based treatments but are inadequately responding to the treatments and consequently have persistent symptoms and disability.
2. Resistance to treatment, which refers to the situations where people have access to treatment but are non-adherent or are disengaged.

This description highlights the importance of considering treatment engagement and adherence when incomplete recovery is observed. Both types of incomplete recovery need to be addressed in order to maximise rates of recovery in young people with early psychosis.

The importance of addressing incomplete recovery

It is crucial to address incomplete recovery in early psychosis because there is evidence that links early treatment response to favourable outcomes. For example, evidence suggests that early recognition of treatment resistance and subsequent treatment adaptation are related to a greater likelihood of remission,[5] and that remission at 3 months of both positive and negative psychotic symptoms is related to good functional recovery at 2 year follow-up.[6] Further, early response to treatment is the strongest predictor of remission and recovery in first episode schizophrenia.[7]

Clinical experience has shown that managing long-term persistent psychosis or treatment resistance is challenging and not always successful so focusing on early incomplete recovery is paramount to maximise recovery and avoid persistent illness. This is achieved by identifying non-adherence, adapting and augmenting treatment regimens as early as possible using individually-focused, comprehensive assessment and formulation.

Identifying non-adherence, adapting and augmenting treatment regimens early using individually-focused, comprehensive assessment and formulation can help manage incomplete recovery.

The prevalence and predictors of incomplete recovery

The reported prevalence of incomplete recovery from first episode psychosis (FEP) varies (due to varying definitions) but estimates range between 5–45%.[3] For schizophrenia specifically, it is estimated that 20–30% of individuals do not respond sufficiently to an initial trial of antipsychotic trial[8] and treatment resistance at 12 months is evident in at least 10% of FEP cases.[9]

Research has found the following risk factors of incomplete recovery from FEP:[10]

- longer untreated duration of psychosis (DUP)
- poorer premorbid functioning
- severe symptoms
- ongoing substance abuse
- cognitive deficits
- poor insight
- non-adherence with medication
- poor response in first 6–12 weeks
- disengagement from the early psychosis service
- male gender.

Encouragingly, there is evidence that engagement with a comprehensive early psychosis treatment service is a good prognostic indicator.[11]

Principles for managing incomplete recovery in FEP

There are a number of broad principles that clinicians can use to manage incomplete recovery. These are based on the fundamental principles of the early psychosis model. A key principle is for services to work to reduce DUP because research has demonstrated that this will reduce the prevalence of incomplete recovery. Promoting early identification of psychosis, and providing easy and rapid access to appropriate services are mechanisms for reducing DUP. Once a person is linked into an early psychosis service, it is essential that the service is able to assess and begin treatment without delay.

Incomplete recovery should be identified as early as possible, ideally by 3 months after commencing treatment. This allows clinicians to consider the situation prior to symptoms becoming entrenched and the potential to avoid possible toxic effects of ongoing psychosis. Young people who continue to experience psychotic symptoms after 3 months of treatment should be identified in case review and/or supervision meetings, and plans made for review and appropriate interventions.

As with all cases of early psychosis, but especially where there is slower than expected recovery, it is essential to instil hope and convey a sense of optimism that things will improve. Demoralisation in the face of continuing psychosis is a significant risk and complicates recovery-focused treatment.

After detection of incomplete recovery, a comprehensive review of the case assessment and formulation should be undertaken with the aim of gaining a thorough and extensive understanding of the young person, their history, their experience of treatment to date, their social and cultural contexts, and their hopes and aspirations. It is important to look for, and treat any comorbidities, and check that all appropriate investigations have been conducted. This enables a review of diagnosis and the adequacy of the treatment provided so far, and to ensure that any illness factors or barriers to treatment effectiveness can be identified and addressed. Special consideration of substance use is important as this is a very common factor in incomplete recovery from FEP.

Interventions for incomplete recovery

Based on the principles outlined above, a range of strategies are used to manage incomplete recovery from FEP. These will be described in further detail below, along with appropriate examples or practical tips where possible.

Prioritise engagement with the young person

Establishing a good therapeutic relationship with young people is fundamental in successfully treating early psychosis. This is particularly important where recovery is slow or incomplete. These young people may have more difficulty than usual in engaging with the treating team due to ongoing symptoms or social or cultural barriers that may also be influencing their recovery. Significant efforts need to be made by clinicians to engage young people who are experiencing incomplete recovery so that they can develop a collaborative shared understanding of the factors contributing to their mental ill-health.

Case scenario: Maha

Maha, a 21-year-old female of Iranian background, has been coming to the service for 5 months. She continues to experience auditory hallucinations and believes that she is being monitored by cameras in her house and neighbourhood. Maha has been very guarded in therapy sessions and unwilling to discuss the nature of her auditory hallucinations, merely nodding in agreement to the question 'Do you hear voices?'

Slowly, Maha's case manager began to build a rapport with her by being warm and interested in her life. They discussed Maha's relationship with her recently-deceased mother. Eventually, Maha was able to disclose that she was hearing her mother's voice telling her not to take her medication as it would make her sick, and not to talk to mental health workers because they were untrustworthy. Maha revealed that she had never taken her prescribed antipsychotic medication.

After psychoeducation about the nature of psychotic symptoms using first-person accounts, Maha accepted her case manager's suggestion of a carefully monitored, 3-month trial of antipsychotic medication.

Similarly, the crucial role of family and other social connections in supporting a young person's recovery should be remembered. Clinicians need to engage with families, friends and other significant supports to enlist their help to understand the young person's difficulties and strengths. These strengths can then be harnessed with the support from family and friends.

Ensure a thorough assessment has been completed

Detecting incomplete recovery should be a trigger for a comprehensive review of the initial assessment of the young person and their progress to date. This will include ensuring that all appropriate physical investigations have been conducted and results reviewed to eliminate any physical cause for psychosis. Psychometric testing may assist in understanding the young person, and it is essential that a thorough understanding of the young person's social circumstance, including family functioning is obtained. Similarly, a detailed developmental history is required so that a complete picture of the young person's situation can inform decisions about interventions across the entire biopsychosocial spectrum. Finally, the diagnosis and therefore the appropriateness of treatments prescribed to date should be reviewed following comprehensive evaluation of the assessment information.

When incomplete recovery has been detected it is important that clinicians ensure a comprehensive biopsychosocial assessment has been conducted. This should be reviewed, updated and improved to allow treatment recommendations to be re-evaluated.

Ensure that the appropriate pharmacotherapy is being used

It is important to review the use of antipsychotic medication when considering incomplete recovery. Medication that the young person has been prescribed for psychosis and its effectiveness needs to be reviewed to ensure that they have received adequate doses of appropriate medication. It is recommended that young people with FEP are prescribed an initial second generation antipsychotic medication (SGA) for 6 weeks and then, if psychotic symptoms have not remitted, switched to another SGA. For a more detailed explanation of the recommended pharmacological treatments in FEP, please see the ENSP manual: *Medical management in early psychosis: a guide for medical practitioners.*

Target medication non-adherence

It is important to review young people's adherence to their medication regimen when managing incomplete recovery because non-adherence with pharmacotherapy is extremely common in all branches of medicine.

Non-adherence with pharmacotherapy has particular risks in psychosis and is often the reason behind cases of incomplete recovery, as illustrated in the case example of Maha above. Considerable research has been devoted to trying to find ways to improve adherence with prescribed medications, and is a topic that receives less time and attention from clinicians than it warrants. A range of factors have been shown to influence medication adherence (see Table 1), and it is important to consider each individual's situation when choosing interventions. Collaborating with young people using a shared decision-making approach to de-stigmatise mental health treatment and empowering them to take responsibility for their wellbeing is an important part of effectively managing incomplete recovery.

Table 1. Factors associated with non-adherence to medication in psychotic illness[12-14]

Age	Beliefs about treatment	Substance use	Service contact frequency
Sex	Past experiences of treatment	Comorbidities	Continuity of care
Education	Past adherence	Potential for spontaneous remission	Duration of care
Race	Self-stigma	Medication efficacy	Adherence monitoring
Socioeconomic status	Illness duration	Side effects	Access to different formulations
Knowledge	Illness phase	Dosage frequency	Family support for treatment
Insight	Symptom types and severity	Cost and access	Financial issues
Motivation	Cognitive function	Therapeutic alliance	Transport issues

Interventions for non-adherence fall into two broad categories: pharmacological and psychosocial.

Pharmacological interventions

Addressing non-adherence to prescribed antipsychotic medication requires optimising pharmacotherapy by working with the young person to find the best medication to treat their symptoms while minimising any side effects, this includes finding the lowest effective dose. This means that there must be close communication and collaboration between the young person, the treating team and other significant supports to understand the overall effect of the medication. Clinicians should also consider the young person's attitude and preferences regarding medication. Using a shared decision-making approach will help find the best treatment for the young person and enhance adherence to this. For more information, please see the clinical practice point *Shared decision making.*

Long-acting injectable (LAIs) antipsychotic medications were developed as the ideal remedy for poor adherence in psychotic disorders and proposed to offer the following benefits over oral medication:[12]

- reduced family conflict around taking medication
- guaranteed delivery of medication
- stable blood levels
- clear signalling of non-adherence.

However, there is ongoing debate about the efficacy of LAIs with recent evidence from randomised controlled trials failing to indicate a superiority of LAIs over oral medication in reducing relapse rates or promoting recovery.[15] This is in contrast to several naturalistic studies that have demonstrated superiority for LAIs in reducing rehospitalisation rates.[12] It has been suggested that people do not stay on LAIs for very long and that this may partially explain these results. Given their uncertain superiority, it is imperative that LAIs only be used with young people with early psychosis with their fully informed consent and where there is a good clinical reason to do so.

Psychosocial interventions for non-adherence

Psychological interventions targeting non-adherence to medications include: psychoeducation, cognitive-behavioural therapy (CBT) and motivational interviewing. Results of studies investigating the effectiveness of these interventions have been mixed, with some studies showing benefits of treatment on adherence, treatment acceptance and insight but others failing to do so. Multifaceted interventions combining CBT, family interventions and community-based approaches appear to be the most successful.[16]

Persistent positive symptoms

The majority of work in incomplete recovery in psychosis has been around persistent positive psychotic symptoms because this was how the concept was originally defined. There was also a lack of recognition of the other symptoms of psychosis: functional outcomes and symptoms beyond positive psychotic symptoms.

Pharmacological strategies

A common response to incomplete remission of positive psychotic symptoms is to increase the dose of antipsychotic medication or to introduce a second antipsychotic agent. However, evidence suggests that an increase in antipsychotic dose above a moderate level is of little benefit, and currently, there is no support for the efficacy of using combinations of antipsychotic medications, thus antipsychotic monotherapy is strongly preferred.[17] Instead, when response to an antipsychotic medication is considered suboptimal, it is recommended that the antipsychotic medication be changed to one with a different receptor profile that may be better suited to the individual.

It is also recommended that clozapine be introduced early in the course of incomplete recovery from psychosis. Clozapine should be considered when symptoms persist despite the sequential use of two SGAs (at effective doses) for at least 6–8 weeks. Clozapine has been shown to be effective for both positive and negative persistent symptoms of psychosis. While many antipsychotic medications are thought to have 'mind-dulling' effects linked with negative symptoms, clozapine does not seem to have this effect. In addition, there is a low risk of extrapyramidal side effects from clozapine.

Although clozapine is considered the most efficacious of antipsychotic available, its use is restricted to those with incomplete response or intolerance of other antipsychotic medications due to the risk of agranulocytosis. Agranulocytosis is an acute disease characterised by a dramatic decrease in the production of granulocytes (mature white blood cells) which means that the body is susceptible to infections. This risk requires haematological monitoring on a weekly basis for the first 6 months, and monthly thereafter, to ensure that clozapine can continue to be used safely.

Beyond pharmaceutical agents, there is considerable interest, research activity and emerging support for the use of anti-inflammatory agents such as aspirin, N-acetylcysteine (NAC) and omega-3 fatty acids (fish oil) to augment antipsychotic treatments.[18,19]

Psychological strategies

Persistent positive psychotic symptoms are usually difficult for young people to cope with and can lead to feeling hopeless and disillusioned with treatment. There may be the sense that things will never improve, and powerful feelings of loss about both their future and former self. It is extremely important that clinicians convey a sense of hope for recovery and enhance coping strategies with every young person. Collaboratively exploring the young person's experience of psychosis in a non-judgmental manner engages them and reassures them that their problems are being taken seriously.

Psychological therapy for persisting positive psychotic symptoms aims to foster the belief that it is possible to manage and tolerate psychotic symptoms. Further, therapy can assist young people to gain awareness of, and control over, things that trigger or exacerbate symptoms. These may be internal or external events that the young person can learn to exert an influence over and, therefore, regain some power over their experience.

Psychological therapy for persistent positive psychotic symptoms draws on psychoeducation, CBT principles and the personal meaning of psychosis for the individual. Components include:

- developing a strong therapeutic relationship between the therapist and the young person
- developing a thorough understanding of the young person's history, illness onset, beliefs, aspirations, explanatory model of psychosis, and the impact of the psychotic illness
- providing psychoeducation about substance use, other comorbidities, psychotic symptoms and the interactions between them
- discussing the stress–vulnerability model of psychosis and normalising explanations of psychotic experiences
- developing coping strategies (both cognitive and behavioural) for positive psychotic symptoms
- working with beliefs about psychotic symptoms to reduce their impact, and examining alternative explanations
- using behavioural experiments to test explanations and develop better awareness and management of emotional arousal
- working to understand the personal relevance and meaning of symptoms.

Persistent negative symptoms

Persistent negative symptoms have received less attention than positive symptoms but are beginning to be the focus of research efforts. Hovington et al found that persistent negative symptoms are present in about 27% of people with FEP.[20] However, the authors noted that definitions of persistent negative symptoms varied and included: severity, duration and aetiology, thus hampering efforts to characterise this problem and develop appropriate treatments. It is important to assess and treat persistent negative symptoms as they are consistently associated with poor functioning 1 year after beginning treatment.

Pharmacological strategies

Although there are currently no widely accepted medications for negative symptoms, considerable research is being undertaken and promising suggestions are emerging. Amisulpride has the most evidence supporting its effectiveness as an antipsychotic monotherapy to treat negative symptoms.[21] The other strategy commonly employed is to add one of a number of promising agents as an adjunct to the currently used antipsychotic treatment. Modest evidence supports the use of adjunctive antidepressant therapy, and there is limited but growing evidence for other agents (minocycline, modafinil, armodafinil and galantamine, see Arango, Garibaldi and Marder for review).[21] There are also non-pharmacological experimental treatments being developed such as transcranial magnetic stimulation and direct current stimulation with some initial promising findings. The treatment of negative psychotic symptoms is a rapidly advancing field and stronger recommendations are likely to appear in the near future.

Clinical experience at EPPIC in Melbourne suggests the following steps in approaching persistent negative symptoms in FEP.

1. Carefully assess whether persisting positive symptoms are responsible for the appearance of negative symptoms. For example, ongoing paranoia may explain inactivity and reluctance to leave the home. It is important to review whether there has been an initial response to treatment, or whether positive symptoms are persisting.
2. Check for extrapyramidal side effects as these can include slowing of mind and activity.
3. Check for depression and treat if present using psychological or pharmacological therapy, or both.
4. Consider treating depression even if not clearly present. Antidepressant medications have shown efficacy for negative symptoms, and depression may be present but undetected.
5. Trial amisulpride as substitute or additional antipsychotic.

Psychological strategies

Careful and thorough psychological assessment of persistent negative symptoms will help clinicians formulate the psychological factors underpinning the negative symptoms and provide treatment targets. Social withdrawal may be an understandable, self-protective reaction to overwhelming anxiety, blunting may be to avoid distress, and there may be strong avoidance in the face of continuing positive psychotic symptoms. Demoralisation and hopelessness can be due to fear, guilt, shame, and stigma can underlie extreme inactivity. All of these may manifest as negative symptoms and be targeted within psychological therapy.

The relationship and rapport between the clinician and young person is paramount; therefore, session length, pace, location and frequency may need to be adapted when severe negative symptoms are present to cope with response latency and cognitive deficits.

Developing a formulation that incorporates a hypothesis about the negative symptoms forms the basis of therapy, and provides the framework and rationale for interventions. Clinicians should repeatedly communicate a sense of optimism and realistic hope for recovery when working with young people around incomplete recovery.

Elements that can be included in psychological work to address negative symptoms are presented in Box 1.

Box 1. Components in psychological work to help manage negative symptoms of psychosis

The following components can be included to manage negative symptoms of psychosis:

- enhancing knowledge of self as distinct from the psychotic illness (e.g. what else is the young person about?)
- recognising personal strengths and identity
- challenging self-defeating beliefs
- addressing stigma about mental illness
- gradually increasing exposure to anxiety provoking and challenging situations
- enhancing coping skills repertoire
- building structure and pleasurable activities gradually into daily routine
- addressing comorbidities such as depression, post-traumatic stress disorder and substance use problems.

> “Persistent negative symptoms are the hardest to deal with because they usually involve low motivation and energy. You have to get to know the young person and their history really well. You need to talk to their family so that you can try to tap into things they have enjoyed … and get them doing those things again. You have to be really positive about them recovering but also let them know that it takes time.

Senior Clinician
EPPIC, Orygen Youth Health Clinical Program

Psychosocial interventions

Case management tasks that address quality and meaningfulness of life are also important in combatting persistent psychotic symptoms (both positive and negative). People need to have adequate housing and finances, and meaningful activities to be fully healthy, and it is likely that this is also integral to achieving recovery from psychosis. Moreover, under the broader banner of psychosocial interventions, very recent evidence is emerging about the benefits of physical exercise for people with enduring psychosis. Positive results for an exercise intervention have been reported by Kahn and Sommer.[22]

Service-level response – the TREAT example from EPPIC, Melbourne

With the overarching goal of providing early intervention for psychosis to minimise disability and maximise recovery, EPPIC has found it valuable to develop a specialised subprogram to address incomplete recovery. Termed the Treatment Resistance Early Assessment Team (TREAT), this subprogram developed a framework for managing young people who experienced prolonged recovery from FEP. TREAT comprises a multidisciplinary team of senior clinicians with expertise and interest in the biological, psychological and social aspects of persistent psychotic symptoms.

TREAT encourages the early detection of incomplete recovery through the clinical review system from 3 months after service entry and the monitoring of those considered to be at risk. Presenting the case to the panel at approximately 6 months of persistent symptoms facilitates a comprehensive case and treatment review. This also supports the treating team to implement assertive and systematic, guideline-concordant treatment. Recommendations are made regarding ongoing treatment across the biopsychosocial domains with the aim of accelerating recovery. This may include expanding the treatment team to include senior clinical specialists (e.g. family specialist or a senior clinical psychologist), which helps develop expertise in working with complex cases. The TREAT review ensures that all components of comprehensive treatment for FEP have been provided to young people and their families, and problem-solves where this has not yet been achieved. There are opportunities for further TREAT reviews so that progress can be monitored and clinicians are supported in helping the young person.

Experience has demonstrated that it is helpful to have all cases of persisting psychosis presented to the TREAT meeting regardless of the putative cause of the ongoing psychosis. It is important that the review process is routine for the service, supported by management and experienced as supportive and collegial by the treating clinicians.

> I was seeing a young man, Jack, who did not seem to be getting better – he still had auditory hallucinations and was not leaving his house except for appointments. I discussed his lack of progress with his doctor and we decided to ask the TREAT panel to review his case. We both attended the meeting and presented our assessment, formulation and the treatment he had had since first coming to the service 6 months ago. The TREAT panel noted the over-protectiveness of Jack's mother and suggested that she be offered some sessions with the family worker. It was also recommended that Jack's medication be changed as he did not seem to be responding to quetiapine.
>
> The doctor and I felt supported by the senior clinicians at TREAT, and Jack had improved (although he still had many problems) when we returned for another TREAT review after 3 months.

Clinician
EPPIC, Orygen Youth Health Clinical Program
talks about Jack and the TREAT experience

Conclusion

Incomplete recovery is an important focus for early psychosis services because early treatment response is predictor of outcome. Enduring psychosis increases the risks of greater functional impairment and damage to social relationships. Incomplete recovery should be detected as early as possible so that concerted efforts can be made to review and adjust treatment offered to avoid developing entrenched persistent psychosis. It is recommended that early psychosis services consider how to detect incomplete recovery in their young people and how best to support clinicians to help their young people recover.

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