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Can antipsychotic dose reduction lead to better functional recovery in first-episode psychosis? A randomized controlled-trial of antipsychotic dose reduction. The reduce trial

Weller, Amber; Gleeson, John; Alvarez-Jimenez, Mario; McGorry, Patrick; Nelson, Barnaby; Allott, Kelly; Bendall, Sarah; Bartholomeusz, Cali; Koval, Peter; Harrigan, Susy; O'Donoghue, Brian; Fornito, Alex; Pantelis, Christos; Paul Amminger, G; Ratheesh, Aswin; Polari, Andrea; Wood, Stephen J; van der El, Kristi; Ellinghaus, Carli; Gates, Jesse

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Can anti-psychotic dose reduction lead to better functional recovery in first episode psychosis? A randomised controlled trial of antipsychotic dose reduction. The Reduce Trial: Study Protocol

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Dose reduction in FEP: Study Protocol

Can anti-psychotic dose reduction lead to better functional recovery in first episode psychosis? A randomised controlled trial of ~~antipsychotic~~anti-psychotic dose reduction. The Reduce Trial: Study Protocol

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Dose reduction in FEP: Study Protocol

Abstract

~~Aim: ~~Anti-psychotic medication has been the mainstay of treatment for psychotic illnesses for over 60 years. This has been associated with improvements in positive symptoms and a reduction in relapse rates. However, there has been little improvement in functional outcomes for people with psychosis. At the same time there is increasing evidence that medications contribute to life shortening metabolic and cardio-vascular illnesses. There is also uncertainty as to the role played by anti-psychotic medication in brain volume changes.

Aim: The primary aim of the study is to compare functional outcomes at 24-months between an anti-psychotic dose reduction strategy with evidence based intensive recovery treatment (EBIRT) (DRS+) and an antipsychotic maintenance treatment with EBIRT (AMTx+).

Methods: A single-blind randomized controlled trial will test the whether ~~a dose reduction strategy in combination with our evidence based intensive recovery treatment (~~DRS~~+),~~+ leads to better vocational and social recovery than ~~continuous antipsychotic maintenance treatment in combination with evidence based intensive recovery treatme~~AMTx~~+)~~+ over a 2-year period in 180 remitted first episode psychosis (FEP) patients. Additionally, we will examine the effect of DRS+ vs AMTx+ on physical health, brain volume and cognitive functioning. ~~In terms of safety this~~This study will also determine whether those receiving DRS+ will be no worse off in terms of psychotic relapses over 2 years follow up.

Results: This paper presents the protocol, rationale and hypotheses for this study which commenced recruitment in July 2017.

Conclusion: This study will test whether an ~~alternative~~antipsychotic dose-reduction recovery treatment leads to improved functioning and safer outcomes in FEP patients. It will also be the first controlled experiment of the effect of exposure to antipsychotic maintenance treatment on brain volume changes in this population.

Key words:

First-episode psychosis

Functional recovery

Dose reduction

Anti-psychotic medication

Protocol

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Dose reduction in FEP: Study Protocol

Introduction

It is over 65 years since antipsychotic medications were introduced and became the mainstay of treatment for psychotic illnesses. ~~There has undoubtedly been many benefits of their use in the control of symptoms, particularly positive symptoms of psychotic illness, and the reduction of relapse rates (Addington, Killackey, & Marulanda, In Press). Despite this, and even with the introduction of second generation antipsychotic medication there has been little indication that people with psychotic illness have returned to functional roles in any great number. For example, people diagnosed with psychotic (Eóin Killackey & Allott, 2013)illnesses are less likely to complete their secondary education(Waghorn et al., 2012) and unemployment remains a highly prevalent problem associated with the disorder. Loneliness is also a significant issue for young people with psychosis, so much so that the onset of psychosis has been characterised as a social network crisis which is not ameliorated by current interventions(Horan, 2006). In a range of other functional domains, housing security,(Harvey, Killackey, Groves, & Herrman, 2012) physical health(V. Morgan et al., 2013), and social relationships and engagement in community(V. A. Morgan et al., 2011), people with psychotic illnesses have worse outcomes than the general population. Antipsychotic medications are effective at addressing the symptoms of illness, but have little to no success at addressing many of the associated problems of the illness~~There has undoubtedly been many benefits of their use in the control of symptoms, particularly positive symptoms of psychotic illness, and the reduction of relapse rates [1]. Despite this, and even with the introduction of second-generation antipsychotic medication there has been little indication that people with psychotic illness have returned to functional roles in any great number. For example, people diagnosed with psychotic illnesses [2] are less likely to complete their secondary education[3] and unemployment remains a highly prevalent problem associated with the disorder. Loneliness is also a significant issue for young people with psychosis, so much so that the onset of psychosis has been characterised as a social network crisis which is not ameliorated by current interventions[4]. In a range of other functional domains, housing security,[5] physical health[6], social relationships and engagement in community[7], people with psychotic illnesses have worse outcomes than the general population. Antipsychotic medications are effective at addressing the symptoms of illness but have little to no success at addressing many of the associated problems of the illness~~(Alvarez-Jimenez et al., 2016)~~[8]. Yet, it is these problems that people living with psychosis most want ~~most~~ addressed~~(Ramsay et al., 2011)~~[9].

Data from ~~studies~~papers published over the last ~~5~~11 years~~(Wunderink, Nieboer, Wiersma, Sytema, & Nienhuis, 2013; Wunderink et al., 2007)~~[10,11] have raised the question of how the best balance or

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"sweet-spot" is struck between exposure to antipsychotic medication, symptomatic improvement, the minimisation of iatrogenic harm and maximising functional recovery~~(Correll, Rubio, & Kane, 2018).~~[12]. The study described in this paper seeks to answer this question.

Background

~~After remission from acute symptoms of psychosis is achieved, most treatments for psychosis have focussed upon the prevention of psychotic relapse (N. Andreasen et al., 2005; Program, 2016). Relapse prevention is a worthy clinical goal, due to the potential for distress and other risks associated with acute symptoms, the direct cost of multiple hospital visits associated with relapse(Knapp et al., 2013), as well as relapsing courses of psychosis being up to 4 times more expensive than non-relapsing courses (Almond, Knapp, Francois, Toumi, & Brugha, 2004; Ascher-Svanum et al., 2010). Less focus has been placed on improving social and vocational functioning despite these being the primary goals of people who experience psychosis~~After remission from acute symptoms of psychosis is achieved, most treatments for psychosis have focussed upon the prevention of psychotic relapse [13,14]. Relapse prevention is a worthy clinical goal, due to the potential for distress and other risks associated with acute symptoms, the direct cost of multiple hospital visits associated with relapse[15], as well as relapsing courses of psychosis being up to 4 times more expensive than non-relapsing courses [16,17]. Less focus has been placed on improving social and vocational functioning despite these being the primary goals of people who experience psychosis~~(Iyer, Mangala, Anitha, Thara, & Malla, 2011; Ramsay et al., 2011)~~[9,18]. For this reason, ~~as well as being the cause of 50% of the total illness costs,~~ functional recovery of people with psychotic illness warrants further attention~~(Alvarez-Jimenez et al., 2016).~~ In this context we define functional recovery to mean- age appropriate vocational functioning, having social outlets, such as friends beyond ~~ones~~one's immediate family and participation in ~~ones~~one's community through such activities as voting.

The impact of antipsychotic maintenance treatment

~~Current evidence based treatment guidelines recommend antipsychotic maintenance treatment for 2-5 years after a First Episode of Psychosis (FEP) (Program, 2016), followed by annual review(Program, 2016). In reality, maintenance treatment can continue for decades (N. C. Andreasen, Liu, Ziebell, Vora, & Ho, 2013), partly due to the lack of clarity and evidence around how long individuals should receive antipsychotic treatment(Program, 2016; Sohler et al., 2016). The goal of current guidelines is to prevent symptomatic relapse rates in FEP clients~~Current evidence based treatment guidelines recommend antipsychotic maintenance treatment for 2-5 years after a First Episode of Psychosis (FEP) [13], followed by annual review[13]. In reality, maintenance treatment can continue for decades[19], partly due to the lack of clarity and evidence around how long individuals should receive

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antipsychotic treatment[13,20]. The goal of current guidelines is to prevent symptomatic relapse rates in FEP clients[(Chen et al., 2010; Emsley, Chiliza, & Asmal, 2013)21,22]. Arguments in favour of ongoing maintenance treatment are that: in the absence of medication, risk of relapse rises significantly, episodes of relapse tend to become longer after the initial episode[(Emsley, Chiliza, & Asmal, 2013)22; response to medication takes longer; and approximately 14% at each relapse will not respond to medication(Emsley, Chiliza, Asmal, & Harvey, 2013). While maintenance treatment is generally successful at treating positive psychotic symptoms(Sohler et al., 2016), the associated side-effects of antipsychotic medication can be a case of significant harm. These side-effects include weight gain [(Grundy, Brewer, Cleeman, Smith, & Lenfant, 2004; Klemp et al., 2011)], sexual dysfunction(Program, 2016) and possible contribution to poor functional recovery in [(Wunderink et al., 2013)]people with positive symptom remission. These associated side-effects can result in poor medication adherence(Coldham, Addington, & Addington, 2002). In fact adherence to antipsychotic medication is poor in FEP; around 60% of them have either non adherence or poor adherence. Further implications of maintenance treatment include metabolic disturbances which lead to increased risks for cardiovascular disease and diabetes[(De Hert et al., 2011)]. One consequence of this is the 20-30 year reduction in life expectancy in people with psychosis [(Olfson, Gerhard, Huang, Crystal, & Stroup, 2015; Subotnik, Nuechterlein, Ventura, & Marder, 2011)]. Metabolic and cardiovascular illness, in large part due to antipsychotic medication[(De Hert et al., 2011)], accounts for the majority of this mortality. (Hage et al., 2018)

; response to medication takes longer; and approximately 14% at each relapse will not respond to medication[23]. While maintenance treatment is generally successful at treating positive psychotic symptoms[20], the associated side-effects of antipsychotic medication can be a case of significant harm. These side-effects include weight gain [24,25], sexual dysfunction[13] and possible contribution to poor functional recovery in [10]people with positive symptom remission. These associated side-effects can result in poor medication adherence[26].Adherence to antipsychotic medication is poor in FEP; around 60% of them have either non adherence or poor adherence[27]. Further implications of maintenance treatment include metabolic disturbances which lead to increased risks for cardiovascular disease and diabetes and the potential for a 20-30 year reduction in life expectancy in people with psychosis[28,29,30]. Metabolic and cardiovascular illness, in large part due to antipsychotic medication[28], accounts for the majority of this mortality. [31]

In addition, maintenance treatment studies[(Waghorn et al., 2012)3] and meta-analyses[(Alvarez-Jimenez, Parker, Hetrick, McGorry, & Gleeson, 2011)32] over the last 10 years have found a relationship between exposure to antipsychotic medication and changes in brain volume. Recent

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cross-sectional evidence indicates that antipsychotic medications may produce reductions in grey and white matter volumes~~(Alvarez-Jimenez et al., 2011)~~[32] ~~(Bola & Mosher, 2002).~~[33]. One study in particular found medicated FEP patients to display significant cortical thinning in the dorsolateral prefrontal and temporal cortices when compared to unmedicated FEP patients, who had cortical thickness measures similar to controls~~(Lesh et al., 2015).~~[34]. Moreover, a 7-year longitudinal neuroimaging study in FEP showed that loss of brain tissue occurs at the rate of 0.~~56cc~~56 cubic centimetres in patients receiving an average of 4mg/day of haloperidol (dose equivalent) over a 1-year period~~(N. C. Andreasen et al., 2013).~~[19]. Intensity in dose years of antipsychotic treatment was associated with reductions in total cerebral volume as well as frontal lobe and white matter volumes. However, without a control group this study could not establish whether brain volume reductions are a direct consequence of maintenance treatment or ~~rather~~ are accounted for by other illness-related factors. Given that early psychosis is associated with significant loss of grey matter volume over time relative to healthy controls~~(Bowie, McLaughlin, Carrion, Auther, & Cornblatt, 2012)~~[35] , there is a possibility that medication discontinuation could reduce this loss, or preserve brain changes such that they are comparable to neurotypical same-age peers. Further, some evidence suggests that antipsychotic treatment may alter cerebral function in FEP~~(Lesh et al., 2015; Lui et al., 2010) (Radua et al., 2012; Sarpal et al., 2015)~~ and the impact of a dose reduction strategy on functional connectivity of resting-state neural networks is currently unknown~~.~~[34,36-38]. Additionally, cognitive function may be adversely affected by maintenance treatment. ~~Evidence for this comes from three~~Three naturalistic studies in prodromal and established schizophrenia groups ~~showings~~show a relationship between level of exposure to antipsychotic medication and decline in cognitive function over time~~(Faber, Smid, Van Gool, Wiersma, & Van Den Bosch, 2012; Husa et al., 2014; Weickert et al., 2013)~~[39-41]~~. As symptom intensity or persistence may confound this relationship~~. Furthermore, meta-analytic evidence suggests that the processing speed impairment observed in psychotic disorders is significantly associated with chlorpromazine equivalent daily dose.[42] As symptom intensity or persistence may confound the relationship between cognitive performance and antipsychotic dose, randomised controlled trials are required.

~~A recent small (N=53) guided anti-psychotic discontinuation RCT in FEP found that cognitive function improved in remitted FEP clients who received guided discontinuation compared with those who received maintenance treatment over a five month follow-up period(Faber et al., 2012). These differences may be explained by the fact that antipsychotic dopamine blockade can lead to impaired verbal learning in psychosis(Weickert et al., 2013). If the positive impact of maintenance/reduced antipsychotic treatment combined with psychosocial treatment on the brain's structure can be~~

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~~confirmed, we will investigate whether attenuation of brain volume reductions acts as a mediator/moderator of psychosocial functioning (Bola & Mosher, 2002; Patrick McGorry, 2005).~~

~~This is in line with previous research that has also shown that adherence to high/standard-dose maintenance treatment is associated with poorer psychosocial functioning early in the course of recovery, suggesting that a strong focus on high-dose maintenance medication may interfere with long-term recovery (Wunderink et al., 2013). This is also consistent with the follow-up results from the Episode II trial(J. F. Gleeson et al., 2009).~~

~~Although maintenance treatments for psychotic illnesses significantly reduce relapse rates compared with placebo, they do not achieve the functional goals of people who experience psychosis.~~

Two small double-blind placebo-controlled crossover studies of inpatients with schizophrenia (N=27 and N=19, respectively) found that antipsychotic medication was associated improved cognitive performance compared with placebo[43,44]. A recent guided anti-psychotic discontinuation RCT in FEP (N=53) found that cognitive function improved in remitted FEP clients who received guided discontinuation compared with those who received maintenance treatment over a five month follow up period[40]. Previous research has also shown that adherence to high/standard-dose maintenance treatment is associated with poorer psychosocial functioning early in the course of recovery, suggesting that a strong focus on high-dose maintenance medication may interfere with long-term recovery [10]. This is also consistent with the follow-up results from the Episode II trial[45].

A recent critical review also proposed that although anti-psychotic maintenance may be efficacious in mid-term treatment of psychosis, there is a paucity of evidence supporting the efficacy of this treatment approach in the long-term, this supports further investigation of a dose reduction strategy[12].

Is dose reduction the answer?

The negative impacts of long--term maintenance have raised the question of whether dose reduction might be associated with better outcomes for individuals affected by psychotic disorders. Recent evidence showing that functioning improves with a strategy to reduce the dose of antipsychotic medication suggests that functional recovery may be suppressed by long-term exposure to antipsychotic medication~~(P. D. McGorry, Alvarez-Jimenez, & Killackey, 2013; Wunderink et al., 2013)~~[10,46]. A meta-analysis of RCTs of antipsychotic treatments in FEP clients showed that approximately 40% of placebo-treated FEP clients had not relapsed at 1-year follow up~~(Alvarez-Jimenez et al., 2011)~~[32]. Subsequently, one recent RCT revealed that, when compared with continuous maintenance treatment, the discontinuation of maintenance treatment in FEP led to improved recovery at 7 years follow up~~(Wunderink et al., 2013).~~[10]. Importantly, this occurred in the absence of intensive psychosocial treatments that may

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hasten improvement of functioning and prevent relapse[~~(Alvarez-Jimenez et al., 2011)~~ 32]. Thus, recovery may be enhanced or hastened if a dose reduction strategy were combined with intensive evidence based psychosocial interventions. These findings suggest that, despite current guidelines, FEP clients may not require maintenance treatment for the initial recommended two-year minimum period to attain recovery and prevent relapse. Indeed, previous research has shown that it is early functional recovery rather than symptomatic recovery that predicts functional recovery at 7.5 years [~~(Alvarez-Jimenez et al., 2012)~~ 47].

Arguably, patient non-adherence[~~(Gitlin et al., 2001)~~ 48], and planned discontinuation of maintenance treatment both pose risks for relapse after FEP[~~(Alvarez-Jimenez et al., 2012)~~ 47]. However, ~~as~~ reduction in symptoms ~~do~~does not automatically translate into functional gains. Prioritising relapse prevention without also giving full consideration to the implications for functional recovery may compromise the long-term outcomes most valued by those who experience the illness [~~(PD. McGorry, 2007; Ramsay et al., 2011)~~ 9,49].

Management of relapse risk therefore, should be balanced with a focus on functional recovery and the costs of long-term continuous maintenance treatment, including probable enhancement in functioning[~~(Alvarez-Jimenez et al., 2011)~~ 32]. A promising balanced approach to treatment includes a dose reduction strategy, combined with intensive and recovery-focussed psychosocial treatments with vigilant monitoring for early signs of relapse[~~(Carpenter, Appelbaum, & Levine, 2003)~~ 50].

Supplementary to a dose reduction strategy, the use of an evidence-based intensive recovery treatment (EBIRT) should be employed to improve likelihood of overall functional outcomes. In the present study, EBIRT combines two previously trialled interventions. These interventions are Individual Placement and Support (IPS) for vocational recovery and CBT for Relapse Prevention. IPS in addition to specialist FEP treatment has produced significantly better outcomes in gaining employment, hours worked, jobs acquired, and longevity of jobs compared to specialist FEP treatment alone [~~(J. F. Gleeson et al., 2009; E. Killackey, Jackson, & McGorry, 2008)~~ 45,51]. CBT for relapse prevention combined with specialist FEP treatment when compared with specialist FEP treatment alone[~~(J. F. Gleeson et al., 2009)~~ 45], led to a significant reduction in relapse rates at 7-months follow up in FEP clients who met remission on positive symptoms. This effect was sustained at 1 year, and relapse rates were kept to historically low levels beyond this time point (30% at 2.5 years) [~~(J. F. Gleeson et al., 2009; J. F. M. Gleeson et al., 2013)~~ 45,52]. However, these differences were no longer significant at 30-month follow-up.

~~Importantly, 83% of clinicians providing care to people experiencing (Thompson, Singh, & Birchwood, 2016)~~Importantly, 83% of clinicians providing care to people experiencing FEP would

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support a carefully monitored dose reduction strategy after patient relapse, and believe this would improve the quality of life of their clients~~.~~[53]. This further supports the acceptability of a dose reduction strategy, particularly in a FEP setting[48,]~~(National Collaborating Centre for Mental Health, 2014; ORYGEN Youth Health, 2010)~~[54,55]

Aims

The primary aim of the study is to compare functional outcomes between a dose reduction strategy with EBIRT group (DRS+) and an antipsychotic maintenance treatment with EBIRT group (AMTx+) at 24-months follow up.

This study has a range of secondary aims:

1. To compare physical health and metabolic profiles between DRS+ and AMTx+ at 24-months follow up.
2. To compare grey and white matter volume between DRS+ and AMTx+ at 24-months follow up.
3. To compare brain activity during resting-state between DRS+ and AMTx+ at 24 months follow up~~.~~*.
4. To compare cognitive functioning between DRS+ and AMTx+ at 24-months follow up.
5. To compare remission and relapse rates between DRS+ and AMTx+ at 24-months follow up.

*This is a largely exploratory aim, however based on the limited literature in this area we hypothesis that the DRS+ group would display greater resting state functional connectivity than the AMTx+ and healthy control groups

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Primary hypothesis

H1: Remitted FEP patients randomised to DRS+ will achieve superior social and vocational functioning at 24-months follow up, compared with remitted FEP patients randomised to AMTx+.

Secondary hypotheses

H2: Participants randomised to DRS+ will have less reduction in grey and white matter volume than participants randomised to AMTx+ at 24-months follow up.

H3: Degree of antipsychotic exposure will be negatively associated with grey and white matter volume at 24-months follow up. Further, it is expected that change in neural activity during resting state will differ significantly between the DRS+ and AMTx+ groups at 24-months follow-up.

H4: Participants randomised to DRS+ will have better cognitive functioning compared to participants randomised to AMTx+ at 24-months follow up.

H5: Participants in the AMTx group will have experienced fewer relapses at 24-months follow up.

H6: Participants randomised to DRS+ will have significantly better metabolic indices (defined as being within normal parameters) and an improved physical health status at 24-months follow up.

Ethical approval

This study was approved by the Melbourne Health Human Research Ethics Committee (HREC/16/MH/309) in February 2017 and began recruiting participants in July 2017. The trial is registered on the Australian and New Zealand Clinical Trials Registry (12617000870358).

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Methodology

Study Design

This study is a single blinded non-placebo randomised controlled trial where research assistants are blinded to treatment allocation.

Study Setting

This study will be conducted at the Early Psychosis Prevention and Intervention Centre (EPPIC), a sub-program of Orygen Youth Health (OYH). OYH is a youth public mental health service in Melbourne for 15 to 25-year-olds (inclusive). EPPIC is a comprehensive specialist early psychosis program that provides outpatient case management ~~and psychiatric treatment.~~, psychosocial intervention and psychiatric treatment. OYH is co-located with Orygen, the National Centre of Excellence in Youth Mental Health and the Centre for Youth Mental Health, The University of

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Melbourne. EPPIC provides up to 2 years of specialised care after which clients are transferred to another service depending upon the level of care required. A proportion of clients receive follow-up care within primary care settings, while others may continue to require case-management and specialist care and are therefore transferred to the adult mental health service. The Reduce Trial will embed specific resources within EPPIC, including a proportion of one psychiatry registrar position, a Vocational Support Worker and a number of specialist Reduce trial case managers, who will provide the medical oversight, the vocational recovery support and the clinical case management for trial participants, respectively.

Inclusion and Exclusion Criteria

Inclusion and Exclusion Criteria have been designed to reflect 'real-world' characteristics of young people presenting to clinical settings with a FEP.

Inclusion Criteria: (i) Current client of EPPIC; (ii) A confirmed diagnosis of first episode of a DSM 5~~(Association, 2013)~~[56] psychotic disorder or mood disorder with psychotic features~~(Association, 2013; First MB, 2015);~~[56,57]; (iii) Aged 15-25 years (inclusive); (iv) ≥ 3 months of remission on positive symptoms of psychosis in the first year of antipsychotic treatment (participants must currently be taking their prescribed anti-psychotic medication) at EPPIC (a score of ≤3 (mild) on the hallucinations, unusual thought disorder, conceptual disorganisation, and suspiciousness subscale items of the Brief Psychiatric Rating Scale (BPRS)~~(Ventura et al., 1993)~~[58] for the past two weeks and a score ≤3 on the hallucinations, unusual thought content, conceptual disorganisation, and suspiciousness subscales of the BRPS~~(Ventura et al., 1993)~~[58] for the past 3 months based on a systematic clinical file review and collateral information collected from the participant's treating team in EPPIC (as needed); (v) Low suicidality defined as a score of 4 or below on the BPRS~~(Ventura et al., 1993)~~[58] sustained for the past 1-month period prior to baseline; (vi) The young person is willing for a caregiver to be informed about the study and will have at least weekly contact with their caregiver; (vii) Ability to provide written informed consent.

Exclusion Criteria: (i) A documented history of an intellectual disability or IQ <70; (ii) Inability to converse in or read English; (iii) Women who are currently pregnant or breastfeeding; (iv) Neurological disorder~~.~~ (illness of the brain, nerves or spinal cord which could not better explain the presence of psychosis).

Recruitment, Consent, and Enrolment ~~and Randomisation~~

Participants will be recruited into the trial through a number of strategies- including regular case review discussions between the Reduce research assistant (RA) and EPPIC Consultants, direct

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referral to Reduce from EPPIC Clinicians and through the RA attending regular EPPIC team meetings to discuss ongoing eligibility of clients nearing three months of psychotic remission. Potential participants are then approached to take part in the trial by either the RA, Reduce registrar or case manager. They are given ample time to consider the option to take part in Reduce and are encouraged to discuss this with their family, local doctor and other supports. Before being enrolled in the study all participants will provide written and informed consent. In the case of minors, their parent or legal guardian will also be required to provide written and informed consent. After the consent process is complete, a Core Baseline assessment is administered by the research assistant. Eligibility is assessed, using the BPRS~~(Ventura et al., 1993)~~[58] and the SCID-RV~~(First MB, 2015).~~ ~~Participant clinical notes will also be used for collateral information to confirm eligibility. If eligibility is confirmed from the above assessments, participants will be randomised to either AMTx+ or DRS+ at a ratio of 1:1 and randomisation will be stratified by sex assigned~~[57]. Participant medical files and EPPIC clinical files will also be used for collateral information to confirm eligibility

Method of Assigning participants to Treatment Groups and Randomisation

An independent statistician will organise the randomisation. The randomisation will be stratified by sex at birth (male vs. female) and baseline diagnosis (affective vs. non-affective) as these characteristics are associated with key outcomes in this study and any chance imbalances may bias the analysis. ~~Following randomisation, the Non-Core Baseline Assessment will be completed within 3 weeks.~~Participants will be allocated to either the EBIRT (AMTx+) or EBIRT (DRS) treatment groups using randomly permuted blocks of varying size within each stratum, to maintain approximately equal group sizes over time. The randomisation sequences will be concealed within a secured password protected website. On obtaining informed consent of a new participant, the delegated research team member will access this website and enter the participant's details. The delegated research team member will then inform the treating team the randomisation outcomes who will then inform and discuss this with the participant.

A client identification (ID) number will be allocated to clients approached to ascertain their eligibility to participate in the study. Each eligible participant will be allocated to a unique and sequential randomization number.

Healthy Control Group

Because the age range of participants covers a time of significant neurodevelopment, 40 healthy controls aged 15-25 years (inclusive), living in the EPPIC catchment, with no history of mental illness, neurological condition or antipsychotic medication treatment will also be recruited. They will undergo MRI scanning, be cognitively assessed and have physical health indicators measured (except

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bloods) at the same four time points as the DRS+ and AMTx+ groups (baseline, 9-months, 15-months and 24-months). This will provide objective control data to determine whether there are physical health, brain volume and neural activation or cognition changes and if they are related to illness, medication or typical development.

Outcome Measures

The primary outcome measure is the Social and Occupational Functioning Scale~~(Goldman, Skodol, & Lave, 1992) (SOFAS) at 24 -months.~~[59] (SOFAS) at 24 -months. In addition to the primary outcome measure, a number of measures will assess physical health and metabolic profiles, brain volumes/activity, cognitive functioning and remission and relapse rates at 24-months.

Secondary Endpoint measures

Symptomatology

~~Remission and relapse of positive symptoms will be assessed using the expanded Brief Psychiatric Rating Scale(Overall & Gorham, 1962) (BPRS) in treatment groups only. Remission of negative symptoms will be assessed using the Scale for Assessment of Negative Symptoms (SANS)(N.C. Andreasen, 1984).~~

~~Neurocognitive assessments~~

~~A battery of neurocognitive tests including the Brief Assessment of Cognition in Schizophrenia(Keefe et al., 2008)~~Remission and relapse of positive symptoms will be assessed using the expanded Brief Psychiatric Rating Scale[60] (BPRS) in treatment groups only. Remission of negative symptoms will be assessed using the Scale for Assessment of Negative Symptoms (SANS)[61]. The a priori clinically significant degree of difference on duration of relapse is 7 days, in accordance with published duration criteria[52].

Neurocognitive assessments

A battery of neurocognitive tests including the Brief Assessment of Cognition in Schizophrenia[62] (BACS App) will be used to assess cognitive functioning in all groups, including healthy controls. Further detail of the full neurocognitive battery can be found in the Schedule of Assessments (Table 1).

INSERT TABLE 1 ABOUT HERE

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Physical health assessments

Blood pressure, weight, height and waist circumference will also be recorded in all groups including healthy controls.

Haematological investigations

Physical health will be measured by clinical blood analysis evaluating fasting glucose, haemoglobin A_{1C}, triglycerides and ~~lipid levels~~Total HL cholesterol in the treatment groups only.

Brain imaging

Brain volume will be quantified in both treatment groups and healthy controls by high-resolution magnetic resonance imaging (MRI). In addition to structural MRI, functional resting state data will also be collected.

Study Intervention

Intervention

After randomisation and allocation to one of the two conditions, all participants will commence the intensive EBIRT phase in which they will attend up to twice weekly individual therapy and vocational support sessions until Month 9.

Evidence-Based Intensive Recovery Treatment (EBIRT)

EBIRT combines two well-validated and manualised psychosocial interventions: Individual Placement and Support (IPS) for vocational recovery and Cognitive Behaviour Therapy (CBT) for Relapse Prevention. EBIRT will be delivered in two phases; a 9-month intensive phase which entails up to two sessions of individual therapy (one CBT sessions and one IPS session) per week for 9-months~~,~~. All participants will receive 9 months of the EBIRT intensive phase. This will followed by a 6-9 month (dependent on tenure remaining in service~~))~~ - maintenance/monitoring phase in which individual therapy sessions will be delivered every 4-6 weeks.

The first component of EBIRT is CBT. This will be provided by a therapist trained in CBT and is comprised of six or more modules of therapy delivered over the 9 ~~-~~month intensive period. The six phases of EBIRT intervention include: (1) initiation of vocational intervention (2) formulation and agenda setting; including vocational goal setting; (3) engagement and assessment for recovery and risk for relapse; (4) psychoeducation with a focus on relapse; (5) early warning signs and relapse planning – will also involve family members with participant's consent; and, treatment and progress review (6). Additional optional modules may be drawn upon depending on case formulation and clinical determination in collaboration with the participant include: substance abuse, stress

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management, and co-morbid anxiety and depression at the ~~investigator's~~participant or clinician discretion. The second component of EBIRT is IPS. This will focus on (a) focussed upon competitive employment, education or training as an outcome; and (b) focussed upon immediate job/education searching and will be delivered by a Youth Specialist Vocational Consultant. In tandem with EBIRT, participants will be randomly assigned following baseline assessment to either the DRS+ or AMTx treatment conditions.

DRS will comprise a 9-month EBIRT phase (DRS+). The comparator group will receive AMTx and EBIRT (AMTx+). The EBIRT intervention will be the same in both groups. The AMTx group treatment, including medication prescription will be in accordance with published treatment guidelines. The Reduce trial clinicians will collect data on frequency, content and duration of therapy sessions in order to measure treatment compliance for the duration of the 15-18 month EBIRT treatment.

At Month 9, all participants will transition into the lower intensity monitoring phase of EBIRT in which they will attend individual therapy sessions with their Reduce case manager every 4-6 weeks for a minimum of 6 months. All participants will receive ~~a minimum of~~at least 15 months of ~~EBIRT therapy however they may receive up to~~ total Reduce treatment and a maximum of 18 months, depending on ~~the balance of~~how long their ~~time left in~~psychotic symptoms take to stabilise upon entry into EPPIC. ~~All~~This means that some participants will ~~be entitled to~~ receive a total of 24~~-~~ months of EPPIC treatment whereby, some participants will receive 27 months total EPPIC treatment. Participants are entitled to the full EPPIC treatment package throughout this time and can have the frequency of appointments with EPPIC team increased should there be a clinical indication to do so. Differences in EPPIC treatment will be recorded.

Dose Reduction Strategy (DRS+) group

Participants who are randomised to this arm of the trial will be offered a gradual dose reduction of their antipsychotic medication~~.~~ at their next medical review after randomisation. Medication will be tapered under close medical supervision over 3-months after allocation to the DRS group to minimise the risk of relapse due to abrupt discontinuation. The rate of tapering will be a 25% dose reduction (or as near to 25% as the medication allows) of the pre-reduction dose every month for 3 months, ~~if clinically safe as determined by the EPPIC treating team.~~until the participant reduces a dose that is considered clinically safe, whereby some participants will completely cease taking the antipsychotic medication. This will see some variation in participants' reduction schedule. All data on the rate of dose reduction will be collected by the Reduce clinicians to measure the variations in participant treatment.

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Antipsychotic Maintenance Treatment (AMTx) group

Participants will be prescribed medication as clinically indicated, concordant with the Australian Clinical Practice Guidelines for FEP~~(National Collaborating Centre for Mental Health, 2014; ORYGEN Youth Health, 2010).~~[54,55]. These guidelines recommend the use of the lowest effective dose of atypical antipsychotics.

All trial participants will have access to all components of treatment at EPPIC, including psychiatric care, case management, psychosocial program, acute inpatient care and outreach as clinically indicated.~~(N.C. Andreasen, 1984; Keefe et al., 2008; Ventura et al., 1993)~~[58,61,62]

Safety Measures

Participants will be managed within the EPPIC clinic at OYH. Participants will be monitored by the treating team. Clinical appointments can be held more frequently when clinically indicated. In addition, the BPRS~~(Ventura et al., 1993)~~[58] and SOFAS~~(Goldman et al., 1992)~~[59] scales will administered weekly by the participant's EBIRT Clinician to assess for participant symptomatic relapse, and to measure the acceptability and safety of the prescribed dose. The SOFAS will measure functioning during the 9-month intensive phase. ~~Safety~~These safety assessments will ~~then~~continue to occur every 4-6 weeks up until Month 24 and administered by either the EBIRT Clinician or the Research Assistant.

~~Relapse and~~ Temporary Pause or Complete Discontinuation from DRS+

In the event of symptomatic relapse or worsening of symptoms, and the participant meeting the criteria for relapse described in Table 2, the participant's dose reduction treatment may be temporarily paused.

Table 2 presents the criteria used to define psychotic relapse and will result in a temporary pause from the DRS+ treatment. These relapse criteria have been developed with the aim of reflecting 'real-world' relapse of FEP. Participants must satisfy either Criteria 1, 2 or 3 in combination with 4 to meet relapse criteria.~~(Ventura et al., 1993)~~[58] There is also a 'fail-safe' option should stopping the DRS be clinically indicated.

TABLE 2 HERE

~~If the above criteria are not met but the participant is considered by their treating clinical team to have significantly deteriorated in relation to psychotic symptoms compared to baseline, and clinical response is deemed necessary, they may also be temporarily paused from the DRS+.~~ Participants will

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be monitored by their treating team and study personnel and regularly assessed for relapse, psychotic exacerbations and functioning.

In the event of a temporary pause in the dose reduction strategy the clinical team will ~~make a decision as to~~decide whether the participant should restart their antipsychotic medication or increase their dose. Any changes made will be in consultation with the participant.

If antipsychotic medication is recommenced or if the dose is increased, it will be titrated up until an effective dose is reached. Titration will occur at a pace appropriate to the individual's clinical presentation and should allow adequate time for a response at each dosing interval. In this case, psychiatry registrars will discuss appropriate dose with treating consultants and ensure any changes are documented. If the participant fails to achieve satisfactory recovery defined by persistence of severe psychotic symptoms whilst consistently meeting criteria described in Table 2 for 3 months following the initial relapse, or if they become pregnant during the study they will be completely discontinued from DRS+, whilst still remaining in EPPIC and receiving EBIRT. These participants will also be invited to continue with the research assessments and included in intention-to-treat analyses.

Table 3 outlines the study schema

TABLE 3 HERE

Participants discontinued from the AMTx+ group will continue to receive treatment in accordance with the Australian Clinical Practice Guidelines ~~and may choose not to participate in EBIRT.~~ . If they wish they may continue with EBIRT and the research assessments. These participants will also be included in intention-to-treat analyses.

Withdrawal Criteria

A participant will be withdrawn from the study if they choose to no longer participate in the Reduce study voluntarily, ~~fail to achieve satisfactory recovery defined by persistence of severe psychotic symptoms whilst consistently meeting criteria described in Table 2 for 3 months following the initial relapse, or if they become pregnant during the study.~~ A participant will be considered 'withdrawn' from the study in cases where all involvement in the trial is ceased~~.~~ and no further follow up is enacted

Blinding

The delegated study statistician will be blind to treatment allocation. Research assistants (RAs) will also be blind to treatment allocation. The study RAs will be kept blind to treatment allocation using

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the following processes: (a) regular reminders will be sent to clinical staff at EPPIC, regarding the importance of the blind; (b) at the start of each research interview the RA will remind the participants of the importance of the blind; (c) the RA will have restricted access to participants' medical records. The unblinded Project Manager will have access to the participant's medical records and will retrieve and provide study RA's with any information that is required (i.e. for screening). Because the extent and rate of dose tapering in each individual case requires clinical tailoring in response to preceding dose reductions, it is not feasible to utilise a placebo control, so medication treatment will be open-label, with medications chosen by EPPIC psychiatrists.

Statistical methods and determination of sample size

Data analysis will be conducted at the completion of the study (24-months from last patient first visit) and as such there will be no interim analyses conducted. The primary outcome is SOFAS score at two-year follow-up. Calculations of effect size are based on detecting a two-year follow-up effect size of d=0.505, based on our previous relapse prevention studies which found a group difference of this magnitude on the SOFAS at two-year follow-up. Power is set at 0.85, $\alpha = .05$ (two-tailed). The estimated sample size is 144 (n=72 per group). To accommodate an attrition rate of 20%, the target sample size will be 180, or 90 participants per treatment group. Differences on social and vocational functioning measures will be examined using mixed model repeated measures and intention-to-treat analysis~~, which are preferred methods for the analysis of clinical trial data in psychiatry. The a priori clinically significant degree of difference on duration of relapse is 7 days, in accordance with published duration criteria(J. F. M. Gleeson et al., 2013).~~. Between-group differences on vocational status will be examined using logistic regression. Patterns of missing data and missing data mechanisms will be investigated using two approaches; firstly, Little's missing completely at random (MCAR) test will be used to assess the degree to which the data are likely to meet the MCAR mechanism; secondly, prediction of missingness at each of the assessment points will be undertaken using binary logistic regression, with a range of baseline sociodemographic, clinical, and psychopathology variables used to predict the presence or absence of a particular assessment. Likelihood techniques will be used to address missing data. The same statistical models described above will be used to characterise the effects of treatment regimen on grey and white matter volumes. Flexible factorial models will be used to estimate significant within-and between-group activation effects at the whole brain level (using F-tests) to determine the effects of treatment regimen on brain function. A cluster-based permutation approach will be used to identify significant differences satisfying a Family Wise Error rate of .05. Age and sex assigned at birth will be controlled for in all analyses.

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Data Safety Monitoring Board

A Data Safety Monitoring Board will be established in accordance with ICH-GCP Guidelines and the NHMRC's 2018 guidelines on DSMBs.

Trial Status

The study commenced enrolling participants in July 2017. Enrolment is continuing at the time of manuscript submission. The report of the study findings is expected in 2024.

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Dose reduction in FEP: Study Protocol

Table 1

Outline of Schedule of Assessments

	Visit 1 Baseline		Visit 2	Visit 3 End of Intervention		Visit 4 End of Study
	Core Baseline[1] Day -21 to 1	Non- Core Baseline[2] Day 1 to Day 21	9-month + 3 months	15-18 month + 3 months	Phone follow up[3] ± 7 days	24-month ± 28 days
Assessment						
Informed Consent[4]	X					
Inclusion/Exclusion Criteria	X					
Demographics	X		X	X		X
Medical & Psychiatric History		X				
Pregnancy (urine)[5]	X			X		X

[1] Core Baseline assessments may be conducted over a number of visits to allow for 'real-world' scenarios however, must be completed prior to randomisation.

[2] Non-Core Component Baseline assessments may be conducted over a number of visits to allow for 'real-world' scenarios and can be completed up to 3 weeks after randomisation.

[3] Telephone contact every 6 weeks from Month 9-24 to check discontinuation/withdrawal criteria.

[4] Informed consent can be obtained up to 21 days prior to baseline.

[5] In addition to conducting urine pregnancy tests at each baseline and 24-month assessments, participants will also be asked to indicate whether they are pregnant or not during 9-month, 15-month assessments and telephone follow-ups.

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	Visit 1 Baseline		Visit 2	Visit 3 End of Intervention		Visit 4 End of Study
	Core Baseline[1] Day -21 to 1	Non- Core Baseline[2] Day 1 to Day 21	9-month + 3 months	15-18 month + 3 months	Phone follow up[3] ± 7 days	24-month ± 28 days
Assessment						
Concomitant Med. Review[6]		X	X	X	X	X
Treatment Allocation						
Randomisation	X					
Diagnosis						
SCID5-RV (Modules A & B)	X			X		X
Intervention						
Participants in DRS+[7]						
EBIRT[8]	←	———	→	←	- - - - - →	Post intervention Follow up

[6] To maintain blinding of RAs, EBIRT clinicians will review medication adherence weekly (every second session) during the EBIRT intensive phase and every session during the EBIRT maintenance phase. EBIRT clinicians will also check concomitant medications every 6 weeks during the intervention phase (up to minimum of 15 months).

[7] Reduce antipsychotic medication dose by 25% every month for 3 months as clinically indicated.

[8] EBIRT intensive phase: Twice weekly individual therapy sessions to month 9, maintenance/monitoring phase 4-6 weeks individual therapy for a minimum of 6 months. A checklist recording details and items covered in of the EBIRT (CBT) Session will be completed every session by the Clinician and entered directly into the eCRF. The IPS Worker will also complete a checklist recording items covered in every session and enter this in to the eCRF. This data will be used to assess fidelity of EBIRT.

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	Visit 1 Baseline		Visit 2	Visit 3 End of Intervention		Visit 4 End of Study
	Core Baseline[1] Day -21 to 1	Non- Core Baseline[2] Day 1 to Day 21	9-month + 3 months	15-18 month + 3 months	Phone follow up[3] ± 7 days	24-month ± 28 days
Assessment						
Medication Compliance						
Clinician's compliance rating[5]		X	X	X		
MARS[5]		X	X	X		X
Medication side effects						
LUNSERS		X	X	X		X
Symptomatology						
BPRS[9]	X		X	X	X	X
SANS		X	X	X		X
DASS-21		X	X	X	X	X
CDSS		X	X	X		X
IPASE		X	X	X		X
Functioning & Quality of Life						
SOFAS[8]		X	X	X	X	X
Vocational functioning		X	X	X	X	X

[9] In addition to assessment time-points and telephone follow-up, the BPRS and SOFAS will be measured weekly during the intensive phase and at therapy sessions during the maintenance phase for purposes of discontinuation criteria.

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	Visit 1 Baseline		Visit 2	Visit 3 End of Intervention		Visit 4 End of Study
	Core Baseline[1] Day -21 to 1	Non- Core Baseline[2] Day 1 to Day 21	9-month + 3 months	15-18 month + 3 months	Phone follow up[3] ± 7 days	24-month ± 28 days
Assessment						
WHOQoL-BREF		X	X	X		X
ULCALS		X	X	X		X
MHCS		X	X	X		X
The Self-efficacy Scale		X	X	X		X
BPNS		X	X	X		X
Daily functioning and affect						
SEMA[10]		X	X	X		X
Pre-morbidity and Illness						
NOS		X				
Trauma						
CTQ		X				
Metabolic monitoring						
Clinical Bloods[11]		X	X	X		X

[10] SEMA will be used to deliver electronic surveys (to be administered directly after the baseline and follow up assessments (visits 1-4) at 8 time points per day in the waking hours of each participant for a period of 7 days. Only participants who have smartphones will complete these surveys.

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	Visit 1 Baseline		Visit 2	Visit 3 End of Intervention		Visit 4 End of Study
	Core Baseline[1] Day -21 to 1	Non- Core Baseline[2] Day 1 to Day 21	9-month + 3 months	15-18 month + 3 months	Phone follow up[3] ± 7 days	24-month ± 28 days
Assessment						
Blood pressure, height, weight and waist circumference[12]		X	X	X		X
Substance Use						
AUDIT		X	X	X		X
ASSIST		X	X	X		X
Neurocognitive						
WRAT-4		X				
BACS		X	X	X		X
ER-40		X	X	X		X
The Hinting Task		X	X	X		X

[11] Clinical bloods will involve testing for fasting glucose, haemoglobin A_{1C}, ~~and lipid levels (~~fasting triglycerides and fasting total HL cholesterol~~).~~.. Clinical Bloods assessment to be completed within two weeks of randomisation and within two weeks of Visits 2 to 4.

[12] Blood pressure, height, weight and waist circumference will also be measured at approximately 12, 18, and 21 months in addition to study visits. These will be measured by study RAs.

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	Visit 1 Baseline		Visit 2	Visit 3 End of Intervention		Visit 4 End of Study
	Core Baseline[1] Day -21 to 1	Non- Core Baseline[2] Day 1 to Day 21	9-month + 3 months	15-18 month + 3 months	Phone follow up[3] ± 7 days	24-month ± 28 days
Assessment						
PAL		X	X	X		X
Edinburgh Handedness Inventory		X				
NSSR		X	X	X		X
PDQ		X	X	X		X
AES		X	X	X		X
Structural and functional Imaging						
Shoulder and Hip width[13]		X				
MRI[14]		X	X	X		X

[13] Eligibility assessment for MRI scan

[14] MRI assessment to be completed within two weeks of randomisation and within two weeks of Visits 2 to 4.

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Table ~~2~~2Temporary Pause from DRS+

1.	Increases from 3 (mild) or below to ratings of 6 or 7 (severe or very severe) on any one of the following 3 BPRS[49] items: (i) unusual thought content, (ii) hallucinations, and (iii) conceptual disorganisation, with a duration criterion of 1 week;
2.	Significant psychotic exacerbations defined by an increase from 3 or below (for at least 1 month) on all the BPRS[49] 3 scales followed by a score of 5 (moderate) on any of the 3-items plus a 2-point increase on one of the other scales (again with the addition of a duration criterion of 1 week) or a rating of 5 on any one of the 3 scales for at least 1 month.
3.	An increase in suicidality as defined by a score of 5 or more on the BPRS[49] Suicidality subscale (i.e., many fantasies about suicide, specific suicide plan, non-lethal attempt) for a duration of at least 1 week.
AND	
4.	A significant decrease in overall functioning as defined by a 20-point drop in SOFAS score from the baseline score, maintained for one month.

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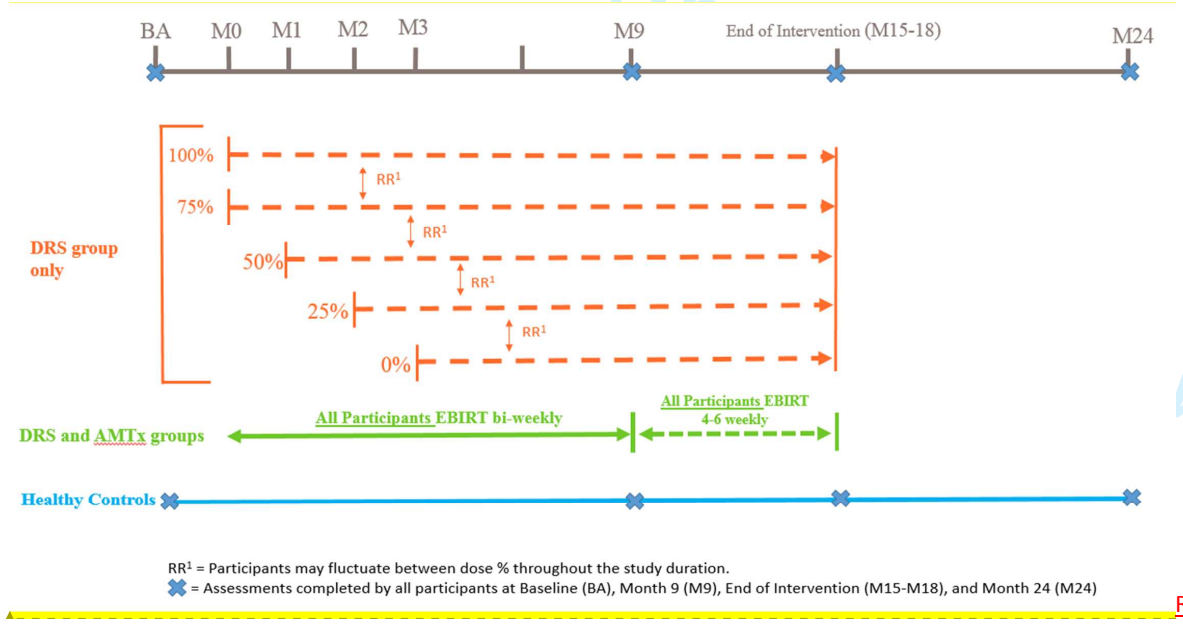
	OR
5.	If the above criteria are not met but the participant is considered by their treating clinical team to have significantly deteriorated in relation to psychotic symptoms compared to baseline, and clinical response is deemed necessary, they may also be temporarily paused from the DRS+.

Table 3



Reduce Intervention Timeline

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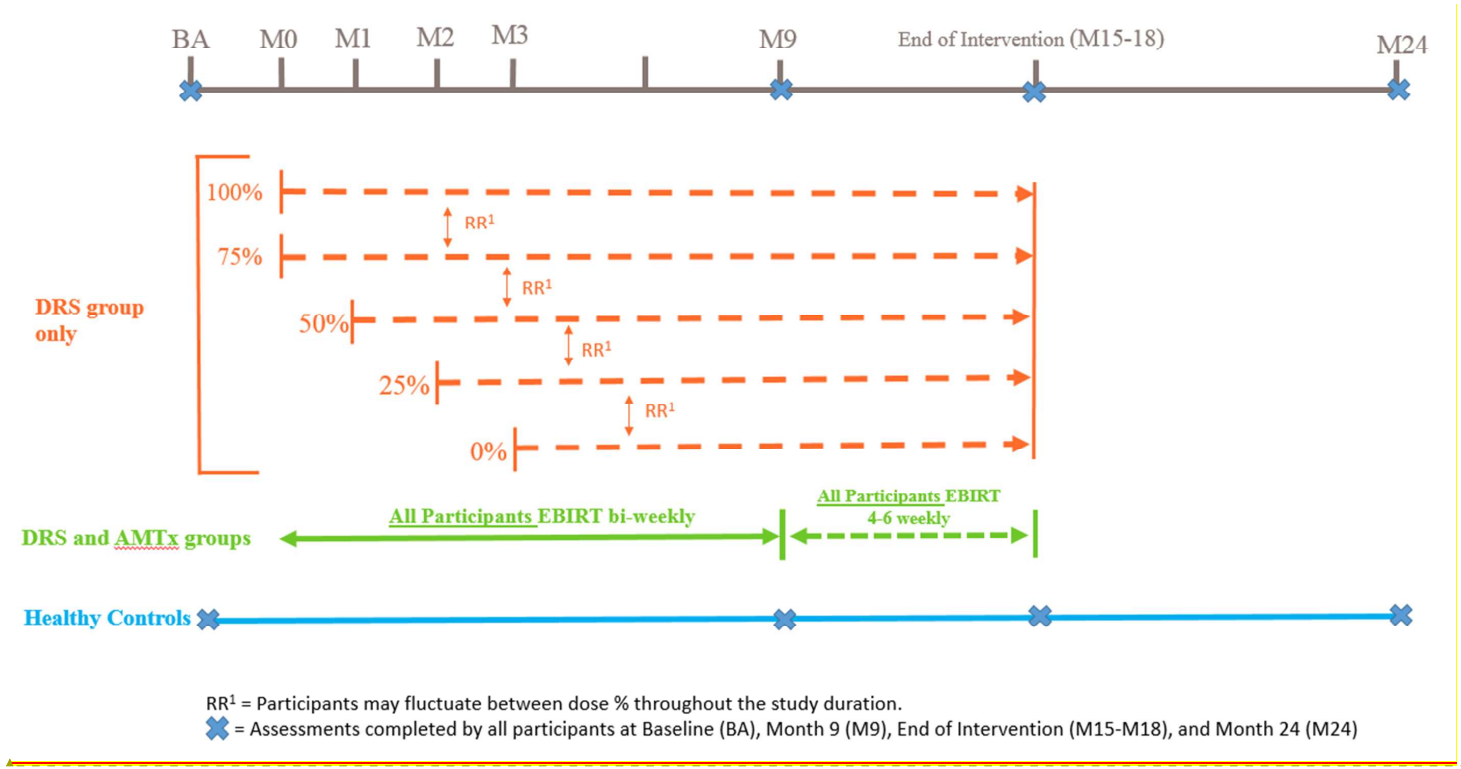

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Can anti-psychotic dose reduction lead to better functional recovery in first episode psychosis? A randomised controlled trial of anti-psychotic dose reduction. The Reduce Trial: Study Protocol

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For Peer Review

Abstract

Anti-psychotic medication has been the mainstay of treatment for psychotic illnesses for over 60 years. This has been associated with improvements in positive psychotic symptoms and a reduction in relapse rates. However, there has been little improvement in functional outcomes for people with psychosis. At the same time there is increasing evidence that medications contribute to life shortening metabolic and cardio-vascular illnesses. There is also uncertainty as to the role played by anti-psychotic medication in brain volume changes.

Aim: The primary aim of the study is, in a population of young people with first episode psychosis, to compare functional outcomes between an anti-psychotic dose reduction strategy with evidence based intensive recovery treatment (EBIRT) group (DRS+) and an antipsychotic maintenance treatment with EBIRT group (AMTx+) at 24-months follow up.

Methods: Our single-blind randomized controlled trial, within a specialist early psychosis treatment setting, will test the whether the DRS+ group leads to better vocational and social recovery than, the AMTx+ group over a 2-year period in 180 remitted first episode psychosis patients. Additionally, we will examine the effect of DRS+ vs AMTx+ on physical health, brain volume and cognitive functioning. This study will also determine whether the group receiving DRS+ will be no worse off in terms of psychotic relapses over 2 years follow up.

Results: This paper presents the protocol, rationale and hypotheses for this study which commenced recruitment in July 2017.

Conclusion: This study will provide evidence as to whether an antipsychotic dose-reduction recovery treatment leads to improved functioning and safer outcomes in first episode psychosis patients. In addition, it will be the first controlled experiment of the effect of exposure to antipsychotic maintenance treatment on brain volume changes in this population.

Key words:

First-episode psychosis

Functional recovery

Dose reduction

Anti-psychotic medication

Protocol

For Peer Review

Introduction

It is over 65 years since antipsychotic medications were introduced and became the mainstay of treatment for psychotic illnesses. There has undoubtedly been many benefits of their use in the control of symptoms, particularly positive symptoms of psychotic illness, and the reduction of relapse rates [1]. Despite this, and even with the introduction of second-generation antipsychotic medication there has been little indication that people with psychotic illness have returned to functional roles in any great number. For example, people diagnosed with psychotic illnesses [2] are less likely to complete their secondary education[3] and unemployment remains a highly prevalent problem associated with the disorder. Loneliness is also a significant issue for young people with psychosis, so much so that the onset of psychosis has been characterised as a social network crisis which is not ameliorated by current interventions[4]. In a range of other functional domains, housing security,[5] physical health[6], social relationships and engagement in community[7], people with psychotic illnesses have worse outcomes than the general population. Antipsychotic medications are effective at addressing the symptoms of illness but have little to no success at addressing many of the associated problems of the illness[8]. Yet, it is these problems that people living with psychosis most want addressed[9].

Data from papers published over the last 11 years[10,11] have raised the question of how the best balance or "sweet-spot" is struck between exposure to antipsychotic medication, symptomatic improvement, the minimisation of iatrogenic harm and maximising functional recovery[12]. The study described in this paper seeks to answer this question.

Background

After remission from acute symptoms of psychosis is achieved, most treatments for psychosis have focussed upon the prevention of psychotic relapse [13,14]. Relapse prevention is a worthy clinical goal, due to the potential for distress and other risks associated with acute symptoms, the direct cost of multiple hospital visits associated with relapse[15], as well as relapsing courses of psychosis being up to 4 times more expensive than non-relapsing courses [16,17]. Less focus has been placed on improving social and vocational functioning despite these being the primary goals of people who experience psychosis[9,18]. For this reason, functional recovery of people with psychotic illness warrants further attention. In this context we define functional recovery to mean- age appropriate vocational functioning, having social outlets, such as friends beyond one's immediate family and participation in one's community through such activities as voting.

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The impact of antipsychotic maintenance treatment

Current evidence based treatment guidelines recommend antipsychotic maintenance treatment for 2-5 years after a First Episode of Psychosis (FEP) [13], followed by annual review[13]. In reality, maintenance treatment can continue for decades[19], partly due to the lack of clarity and evidence around how long individuals should receive antipsychotic treatment[13,20]. The goal of current guidelines is to prevent symptomatic relapse rates in FEP clients[21,22]. Arguments in favour of ongoing maintenance treatment are that: in the absence of medication, risk of relapse rises significantly, episodes of relapse tend to become longer after the initial episode[22]; response to medication takes longer; and approximately 14% at each relapse will not respond to medication[23]. While maintenance treatment is generally successful at treating positive psychotic symptoms[20], the associated side-effects of antipsychotic medication can be a case of significant harm. These side-effects include weight gain [24,25], sexual dysfunction[13] and possible contribution to poor functional recovery in [10]people with positive symptom remission. These associated side-effects can result in poor medication adherence[26].Adherence to antipsychotic medication is poor in FEP; around 60% of them have either non adherence or poor adherence[27]. Further implications of maintenance treatment include metabolic disturbances which lead to increased risks for cardiovascular disease and diabetes and the potential for a 20-30 year reduction in life expectancy in people with psychosis[28,29,30]. Metabolic and cardiovascular illness, in large part due to antipsychotic medication[28], accounts for the majority of this mortality. [31]

In addition, maintenance treatment studies[3] and meta-analyses[32] over the last 10 years have found a relationship between exposure to antipsychotic medication and changes in brain volume. Recent cross-sectional evidence indicates that antipsychotic medications may produce reductions in grey and white matter volumes[32 33]. One study in particular found medicated FEP patients to display significant cortical thinning in the dorsolateral prefrontal and temporal cortices when compared to unmedicated FEP patients, who had cortical thickness measures similar to controls[34]. Moreover, a 7-year longitudinal neuroimaging study in FEP showed that loss of brain tissue occurs at the rate of 0.56 cubic centimetres in patients receiving an average of 4mg/day of haloperidol (dose equivalent) over a 1- year period[19]. Intensity in dose years of antipsychotic treatment was associated with reductions in total cerebral volume as well as frontal lobe and white matter volumes. However, without a control group this study could not establish whether brain volume reductions are a direct consequence of maintenance treatment or are accounted for by other illness-related factors. Given that early psychosis is associated with significant loss of grey matter volume over time relative to healthy controls[35] , there is a possibility that medication discontinuation could reduce this loss, or

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preserve brain changes such that they are comparable to neurotypical same-age peers. Further, some evidence suggests that antipsychotic treatment may alter cerebral function in FEP and the impact of a dose reduction strategy on functional connectivity of resting-state neural networks is currently unknown [34,36-38]. Additionally, cognitive function may be adversely affected by maintenance treatment. Three naturalistic studies in prodromal and established schizophrenia groups show a relationship between level of exposure to antipsychotic medication and decline in cognitive function over time[39-41]. Furthermore, meta-analytic evidence suggests that the processing speed impairment observed in psychotic disorders is significantly associated with chlorpromazine equivalent daily dose.[42] As symptom intensity or persistence may confound the relationship between cognitive performance and antipsychotic dose, randomised controlled trials are required.

Two small double-blind placebo-controlled crossover studies of inpatients with schizophrenia (N=27 and N=19, respectively) found that antipsychotic medication was associated improved cognitive performance compared with placebo[43,44]. A recent guided anti-psychotic discontinuation RCT in FEP (N=53) found that cognitive function improved in remitted FEP clients who received guided discontinuation compared with those who received maintenance treatment over a five month follow up period[40]. Previous research has also shown that adherence to high/standard-dose maintenance treatment is associated with poorer psychosocial functioning early in the course of recovery, suggesting that a strong focus on high-dose maintenance medication may interfere with long-term recovery [10]. This is also consistent with the follow-up results from the Episode II trial[45].

A recent critical review also proposed that although anti-psychotic maintenance may be efficacious in mid-term treatment of psychosis, there is a paucity of evidence supporting the efficacy of this treatment approach in the long-term, this supports further investigation of a dose reduction strategy[12].

Is dose reduction the answer?

The negative impacts of long-term maintenance have raised the question of whether dose reduction might be associated with better outcomes for individuals affected by psychotic disorders. Recent evidence showing that functioning improves with a strategy to reduce the dose of antipsychotic medication suggests that functional recovery may be suppressed by long-term exposure to antipsychotic medication[10,46]. A meta-analysis of RCTs of antipsychotic treatments in FEP clients showed that approximately 40% of placebo-treated FEP clients had not relapsed at 1-year follow up[32]. Subsequently, one recent RCT revealed that, when compared with continuous maintenance treatment, the discontinuation of maintenance treatment in FEP led to improved recovery at 7 years follow up[10]. Importantly, this occurred in the absence of intensive psychosocial treatments that may

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hasten improvement of functioning and prevent relapse[32]. Thus, recovery may be enhanced or hastened if a dose reduction strategy were combined with intensive evidence based psychosocial interventions. These findings suggest that, despite current guidelines, FEP clients may not require maintenance treatment for the initial recommended two-year minimum period to attain recovery and prevent relapse. Indeed, previous research has shown that it is early functional recovery rather than symptomatic recovery that predicts functional recovery at 7.5 years [47].

Arguably, patient non-adherence[48], and planned discontinuation of maintenance treatment both pose risks for relapse after FEP[47]. However, reduction in symptoms does not automatically translate into functional gains. Prioritising relapse prevention without also giving full consideration to the implications for functional recovery may compromise the long-term outcomes most valued by those who experience the illness [9,49].

Management of relapse risk therefore, should be balanced with a focus on functional recovery and the costs of long-term continuous maintenance treatment, including probable enhancement in functioning[32]. A promising balanced approach to treatment includes a dose reduction strategy, combined with intensive and recovery-focussed psychosocial treatments with vigilant monitoring for early signs of relapse[50].

Supplementary to a dose reduction strategy, the use of an evidence-based intensive recovery treatment (EBIRT) should be employed to improve likelihood of overall functional outcomes. In the present study, EBIRT combines two previously trialled interventions. These interventions are Individual Placement and Support (IPS) for vocational recovery and CBT for Relapse Prevention. IPS in addition to specialist FEP treatment has produced significantly better outcomes in gaining employment, hours worked, jobs acquired, and longevity of jobs compared to specialist FEP treatment alone [45,51]. CBT for relapse prevention combined with specialist FEP treatment when compared with specialist FEP treatment alone[45], led to a significant reduction in relapse rates at 7-months follow up in FEP clients who met remission on positive symptoms. This effect was sustained at 1 year, and relapse rates were kept to historically low levels beyond this time point (30% at 2.5 years) [45,52]. However, these differences were no longer significant at 30-month follow-up.

Importantly, 83% of clinicians providing care to people experiencing FEP would support a carefully monitored dose reduction strategy after patient relapse, and believe this would improve the quality of life of their clients[53]. This further supports the acceptability of a dose reduction strategy, particularly in a FEP setting[48,54,55]

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Aims

The primary aim of the study is to compare functional outcomes between a dose reduction strategy with EBIRT group (DRS+) and an antipsychotic maintenance treatment with EBIRT group (AMTx+) at 24-months follow up.

This study has a range of secondary aims:

1. To compare physical health and metabolic profiles between DRS+ and AMTx+ at 24-months follow up.
2. To compare grey and white matter volume between DRS+ and AMTx+ at 24-months follow up.
3. To compare brain activity during resting-state between DRS+ and AMTx+ at 24 months follow up*.
4. To compare cognitive functioning between DRS+ and AMTx+ at 24-months follow up.
5. To compare remission and relapse rates between DRS+ and AMTx+ at 24-months follow up.

*This is a largely exploratory aim, however based on the limited literature in this area we hypothesis that the DRS+ group would display greater resting state functional connectivity than the AMTx+ and healthy control groups

Primary hypothesis

H1: Remitted FEP patients randomised to DRS+ will achieve superior social and vocational functioning at 24-months follow up, compared with remitted FEP patients randomised to AMTx+.

Secondary hypotheses

H2: Participants randomised to DRS+ will have less reduction in grey and white matter volume than participants randomised to AMTx+ at 24-months follow up.

H3: Degree of antipsychotic exposure will be negatively associated with grey and white matter volume at 24-months follow up. Further, it is expected that change in neural activity during resting state will differ significantly between the DRS+ and AMTx+ groups at 24-months follow-up.

H4: Participants randomised to DRS+ will have better cognitive functioning compared to participants randomised to AMTx+ at 24-months follow up.

H5: Participants in the AMTx group will have experienced fewer relapses at 24-months follow up.

H6: Participants randomised to DRS+ will have significantly better metabolic indices (defined as being within normal parameters) and an improved physical health status at 24-months follow up.

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Ethical approval

This study was approved by the Melbourne Health Human Research Ethics Committee (HREC/16/MH/309) in February 2017 and began recruiting participants in July 2017. The trial is registered on the Australian and New Zealand Clinical Trials Registry (12617000870358).

Methodology

Study Design

This study is a single blinded non-placebo randomised controlled trial where research assistants are blinded to treatment allocation.

Study Setting

This study will be conducted at the Early Psychosis Prevention and Intervention Centre (EPPIC), a sub-program of Orygen Youth Health (OYH). OYH is a youth public mental health service in Melbourne for 15 to 25-year-olds (inclusive). EPPIC is a comprehensive specialist early psychosis program that provides outpatient case management, psychosocial intervention and psychiatric treatment. OYH is co-located with Orygen, the National Centre of Excellence in Youth Mental Health and the Centre for Youth Mental Health, The University of Melbourne. EPPIC provides up to 2 years of specialised care after which clients are transferred to another service depending upon the level of care required. A proportion of clients receive follow-up care within primary care settings, while others may continue to require case-management and specialist care and are therefore transferred to the adult mental health service. The Reduce Trial will embed specific resources within EPPIC, including a proportion of one psychiatry registrar position, a Vocational Support Worker and a number of specialist Reduce trial case managers, who will provide the medical oversight, the vocational recovery support and the clinical case management for trial participants, respectively.

Inclusion and Exclusion Criteria

Inclusion and Exclusion Criteria have been designed to reflect 'real-world' characteristics of young people presenting to clinical settings with a FEP.

Inclusion Criteria: (i) Current client of EPPIC; (ii) A confirmed diagnosis of first episode of a DSM 5[56] psychotic disorder or mood disorder with psychotic features[56,57]; (iii) Aged 15-25 years (inclusive); (iv) ≥ 3 months of remission on positive symptoms of psychosis in the first year of antipsychotic treatment (participants must currently be taking their prescribed anti-psychotic medication) at EPPIC (a score of ≤3 (mild) on the hallucinations, unusual thought disorder, conceptual disorganisation, and suspiciousness subscale items of the Brief Psychiatric Rating Scale (BPRS)[58] for the past two weeks and a score ≤3 on the hallucinations, unusual thought content, conceptual disorganisation,

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and suspiciousness subscales of the BRPS[58] for the past 3 months based on a systematic clinical file review and collateral information collected from the participant's treating team in EPPIC (as needed); (v) Low suicidality defined as a score of 4 or below on the BPRS[58] sustained for the past 1-month period prior to baseline; (vi) The young person is willing for a caregiver to be informed about the study and will have at least weekly contact with their caregiver; (vii) Ability to provide written informed consent.

Exclusion Criteria: (i) A documented history of an intellectual disability or IQ <70; (ii) Inability to converse in or read English; (iii) Women who are currently pregnant or breastfeeding; (iv) Neurological disorder (illness of the brain, nerves or spinal cord which could not better explain the presence of psychosis).

Recruitment, Consent, and Enrolment

Participants will be recruited into the trial through a number of strategies- including regular case review discussions between the Reduce research assistant (RA) and EPPIC Consultants, direct referral to Reduce from EPPIC Clinicians and through the RA attending regular EPPIC team meetings to discuss ongoing eligibility of clients nearing three months of psychotic remission. Potential participants are then approached to take part in the trial by either the RA, Reduce registrar or case manager. They are given ample time to consider the option to take part in Reduce and are encouraged to discuss this with their family, local doctor and other supports. Before being enrolled in the study all participants will provide written and informed consent. In the case of minors, their parent or legal guardian will also be required to provide written and informed consent. After the consent process is complete, a Core Baseline assessment is administered by the research assistant. Eligibility is assessed, using the BPRS[58] and the SCID-RV[57]. Participant medical files and EPPIC clinical files will also be used for collateral information to confirm eligibility

Method of Assigning participants to Treatment Groups and Randomisation

An independent statistician will organise the randomisation. The randomisation will be stratified by sex at birth (male vs. female) and baseline diagnosis (affective vs. non-affective) as these characteristics are associated with key outcomes in this study and any chance imbalances may bias the analysis. Participants will be allocated to either the EBIRT (AMTx+) or EBIRT (DRS) treatment groups using randomly permuted blocks of varying size within each stratum, to maintain approximately equal group sizes over time. The randomisation sequences will be concealed within a secured password protected website. On obtaining informed consent of a new participant, the delegated research team member will access this website and enter the participant's details. The

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delegated research team member will then inform the treating team the randomisation outcomes who will then inform and discuss this with the participant.

A client identification (ID) number will be allocated to clients approached to ascertain their eligibility to participate in the study. Each eligible participant will be allocated to a unique and sequential randomization number.

Healthy Control Group

Because the age range of participants covers a time of significant neurodevelopment, 40 healthy controls aged 15-25 years (inclusive), living in the EPPIC catchment, with no history of mental illness, neurological condition or antipsychotic medication treatment will also be recruited. They will undergo MRI scanning, be cognitively assessed and have physical health indicators measured (except bloods) at the same four time points as the DRS+ and AMTx+ groups (baseline, 9-months, 15-months and 24-months). This will provide objective control data to determine whether there are physical health, brain volume and neural activation or cognition changes and if they are related to illness, medication or typical development.

Outcome Measures

The primary outcome measure is the Social and Occupational Functioning Scale[59] (SOFAS) at 24 -months. In addition to the primary outcome measure, a number of measures will assess physical health and metabolic profiles, brain volumes/activity, cognitive functioning and remission and relapse rates at 24-months.

Secondary Endpoint measures

Symptomatology

Remission and relapse of positive symptoms will be assessed using the expanded Brief Psychiatric Rating Scale[60] (BPRS) in treatment groups only. Remission of negative symptoms will be assessed using the Scale for Assessment of Negative Symptoms (SANS)[61]. The a priori clinically significant degree of difference on duration of relapse is 7 days, in accordance with published duration criteria[52].

Neurocognitive assessments

A battery of neurocognitive tests including the Brief Assessment of Cognition in Schizophrenia[62] (BACS App) will be used to assess cognitive functioning in all groups, including healthy controls. Further detail of the full neurocognitive battery can be found in the Schedule of Assessments (Table 1).

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INSERT TABLE 1 ABOUT HERE

Physical health assessments

Blood pressure, weight, height and waist circumference will also be recorded in all groups including healthy controls.

Haematological investigations

Physical health will be measured by clinical blood analysis evaluating fasting glucose, haemoglobin A_{1C}, triglycerides and Total HL cholesterol in the treatment groups only.

Brain imaging

Brain volume will be quantified in both treatment groups and healthy controls by high-resolution magnetic resonance imaging (MRI). In addition to structural MRI, functional resting state data will also be collected.

Study Intervention

Intervention

After randomisation and allocation to one of the two conditions, all participants will commence the intensive EBIRT phase in which they will attend up to twice weekly individual therapy and vocational support sessions until Month 9.

Evidence-Based Intensive Recovery Treatment (EBIRT)

EBIRT combines two well-validated and manualised psychosocial interventions: Individual Placement and Support (IPS) for vocational recovery and Cognitive Behaviour Therapy (CBT) for Relapse Prevention. EBIRT will be delivered in two phases; a 9-month intensive phase which entails up to two sessions of individual therapy (one CBT sessions and one IPS session) per week for 9-months. All participants will receive 9 months of the EBIRT intensive phase. This will followed by a 6-9 month (dependent on tenure remaining in service) - maintenance/monitoring phase in which individual therapy sessions will be delivered every 4-6 weeks.

The first component of EBIRT is CBT. This will be provided by a therapist trained in CBT and is comprised of six or more modules of therapy delivered over the 9-month intensive period. The six phases of EBIRT intervention include: (1) initiation of vocational intervention (2) formulation and agenda setting; including vocational goal setting; (3) engagement and assessment for recovery and

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risk for relapse; (4) psychoeducation with a focus on relapse; (5) early warning signs and relapse planning – will also involve family members with participant's consent; and, treatment and progress review (6). Additional optional modules may be drawn upon depending on case formulation and clinical determination in collaboration with the participant include: substance abuse, stress management, and co-morbid anxiety and depression at the participant or clinician discretion. The second component of EBIRT is IPS. This will focus on (a) focussed upon competitive employment, education or training as an outcome; and (b) focussed upon immediate job/education searching and will be delivered by a Youth Specialist Vocational Consultant. In tandem with EBIRT, participants will be randomly assigned following baseline assessment to either the DRS+ or AMTx treatment conditions.

DRS will comprise a 9-month EBIRT phase (DRS+). The comparator group will receive AMTx and EBIRT (AMTx+). The EBIRT intervention will be the same in both groups. The AMTx group treatment, including medication prescription will be in accordance with published treatment guidelines. The Reduce trial clinicians will collect data on frequency, content and duration of therapy sessions in order to measure treatment compliance for the duration of the 15-18 month EBIRT treatment.

At Month 9, all participants will transition into the lower intensity monitoring phase of EBIRT in which they will attend individual therapy sessions with their Reduce case manager every 4-6 weeks for a minimum of 6 months. All participants will receive at least 15 months of total Reduce treatment and a maximum of 18 months, depending on how long their psychotic symptoms take to stabilise upon entry into EPPIC. This means that some participants will receive a total of 24 months of EPPIC treatment whereby, some participants will receive 27 months total EPPIC treatment. Participants are entitled to the full EPPIC treatment package throughout this time and can have the frequency of appointments with EPPIC team increased should there be a clinical indication to do so. Differences in EPPIC treatment will be recorded.

Dose Reduction Strategy (DRS+) group

Participants who are randomised to this arm of the trial will be offered a gradual dose reduction of their antipsychotic medication at their next medical review after randomisation. Medication will be tapered under close medical supervision over 3-months after allocation to the DRS group to minimise the risk of relapse due to abrupt discontinuation. The rate of tapering will be a 25% dose reduction (or as near to 25% as the medication allows) of the pre-reduction dose every month for 3 months, until the participant reduces a dose that is considered clinically safe, whereby some participants will completely cease taking the antipsychotic medication. This will see some variation

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in participants' reduction schedule. All data on the rate of dose reduction will be collected by the Reduce clinicians to measure the variations in participant treatment.

Antipsychotic Maintenance Treatment (AMTx) group

Participants will be prescribed medication as clinically indicated, concordant with the Australian Clinical Practice Guidelines for FEP[54,55]. These guidelines recommend the use of the lowest effective dose of atypical antipsychotics.

All trial participants will have access to all components of treatment at EPPIC, including psychiatric care, case management, psychosocial program, acute inpatient care and outreach as clinically indicated.[58,61,62]

Safety Measures

Participants will be managed within the EPPIC clinic at OYH. Participants will be monitored by the treating team. Clinical appointments can be held more frequently when clinically indicated. In addition, the BPRS[58] and SOFAS[59] scales will administered weekly by the participant's EBIRT Clinician to assess for participant symptomatic relapse, and to measure the acceptability and safety of the prescribed dose. The SOFAS will measure functioning during the 9-month intensive phase. These safety assessments will continue to occur every 4-6 weeks up until Month 24 and administered by either the EBIRT Clinician or the Research Assistant.

Temporary Pause or Complete Discontinuation from DRS+

In the event of symptomatic relapse or worsening of symptoms, and the participant meeting the criteria for relapse described in Table 2, the participant's dose reduction treatment may be temporarily paused.

Table 2 presents the criteria used to define psychotic relapse and will result in a temporary pause from the DRS+ treatment. These relapse criteria have been developed with the aim of reflecting 'real-world' relapse of FEP. Participants must satisfy either Criteria 1, 2 or 3 in combination with 4 to meet relapse criteria.[58] There is also a 'fail-safe' option should stopping the DRS be clinically indicated.

TABLE 2 HERE

Participants will be monitored by their treating team and study personnel and regularly assessed for relapse, psychotic exacerbations and functioning.

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In the event of a temporary pause in the dose reduction strategy the clinical team will decide whether the participant should restart their antipsychotic medication or increase their dose. Any changes made will be in consultation with the participant.

If antipsychotic medication is recommenced or if the dose is increased, it will be titrated up until an effective dose is reached. Titration will occur at a pace appropriate to the individual's clinical presentation and should allow adequate time for a response at each dosing interval. In this case, psychiatry registrars will discuss appropriate dose with treating consultants and ensure any changes are documented. If the participant fails to achieve satisfactory recovery defined by persistence of severe psychotic symptoms whilst consistently meeting criteria described in Table 2 for 3 months following the initial relapse, or if they become pregnant during the study they will be completely discontinued from DRS+, whilst still remaining in EPPIC and receiving EBIRT. These participants will also be invited to continue with the research assessments and included in intention-to-treat analyses.

Table 3 outlines the study schema

TABLE 3 HERE

Participants discontinued from the AMTx+ group will continue to receive treatment in accordance with the Australian Clinical Practice Guidelines. If they wish they may continue with EBIRT and the research assessments. These participants will also be included in intention-to-treat analyses.

Withdrawal Criteria

A participant will be withdrawn from the study if they choose to no longer participate in the Reduce study voluntarily, A participant will be considered 'withdrawn' from the study in cases where all involvement in the trial is ceased and no further follow up is enacted

Blinding

The delegated study statistician will be blind to treatment allocation. Research assistants (RAs) will also be blind to treatment allocation. The study RAs will be kept blind to treatment allocation using the following processes: (a) regular reminders will be sent to clinical staff at EPPIC, regarding the importance of the blind; (b) at the start of each research interview the RA will remind the participants of the importance of the blind; (c) the RA will have restricted access to participants' medical records. The unblinded Project Manager will have access to the participant's medical records and will retrieve and provide study RA's with any information that is required (i.e. for screening). Because the extent and rate of dose tapering in each individual case requires clinical

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tailoring in response to preceding dose reductions, it is not feasible to utilise a placebo control, so medication treatment will be open-label, with medications chosen by EPPIC psychiatrists.

Statistical methods and determination of sample size

Data analysis will be conducted at the completion of the study (24-months from last patient first visit) and as such there will be no interim analyses conducted. The primary outcome is SOFAS score at two-year follow-up. Calculations of effect size are based on detecting a two-year follow-up effect size of d=0.505, based on our previous relapse prevention studies which found a group difference of this magnitude on the SOFAS at two-year follow-up. Power is set at 0.85, $\alpha = .05$ (two-tailed). The estimated sample size is 144 (n=72 per group). To accommodate an attrition rate of 20%, the target sample size will be 180, or 90 participants per treatment group. Differences on social and vocational functioning measures will be examined using mixed model repeated measures and intention-to-treat analysis. Between-group differences on vocational status will be examined using logistic regression. Patterns of missing data and missing data mechanisms will be investigated using two approaches; firstly, Little's missing completely at random (MCAR) test will be used to assess the degree to which the data are likely to meet the MCAR mechanism; secondly, prediction of missingness at each of the assessment points will be undertaken using binary logistic regression, with a range of baseline sociodemographic, clinical, and psychopathology variables used to predict the presence or absence of a particular assessment. Likelihood techniques will be used to address missing data. The same statistical models described above will be used to characterise the effects of treatment regimen on grey and white matter volumes. Flexible factorial models will be used to estimate significant within- and between-group activation effects at the whole brain level (using F-tests) to determine the effects of treatment regimen on brain function. A cluster-based permutation approach will be used to identify significant differences satisfying a Family Wise Error rate of .05. Age and sex assigned at birth will be controlled for in all analyses.

Data Safety Monitoring Board

A Data Safety Monitoring Board will be established in accordance with ICH-GCP Guidelines and the NHMRC's 2018 guidelines on DSMBs.

Trial Status

The study commenced enrolling participants in July 2017. Enrolment is continuing at the time of manuscript submission. The report of the study findings is expected in 2024.

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For Peer Review

Dose reduction in FEP: Study Protocol

Table 1

Outline of Schedule of Assessments

	Visit 1 Baseline		Visit 2	Visit 3 End of Intervention		Visit 4 End of Study
	Core Baseline[1] Day -21 to 1	**Non- Core Baseline[2] Day 1 to Day 21**	**9-month + 3 months**	**15-18 month + 3 months**	**Phone follow up[3] ± 7 days**	**24-month ± 28 days**
Assessment						
Informed Consent[4]	X					
Inclusion/Exclusion Criteria	X					
Demographics	X		X	X		X
Medical & Psychiatric History		X				
Pregnancy (urine)[5]	X			X		X

[1] Core Baseline assessments may be conducted over a number of visits to allow for 'real-world' scenarios however, must be completed prior to randomisation.

[2] Non-Core Component Baseline assessments may be conducted over a number of visits to allow for 'real-world' scenarios and can be completed up to 3 weeks after randomisation.

[3] Telephone contact every 6 weeks from Month 9-24 to check discontinuation/withdrawal criteria.

[4] Informed consent can be obtained up to 21 days prior to baseline.

[5] In addition to conducting urine pregnancy tests at each baseline and 24-month assessments, participants will also be asked to indicate whether they are pregnant or not during 9-month, 15-month assessments and telephone follow-ups.

For Peer Review

Dose reduction in FEP: Study Protocol

	Visit 1 Baseline		Visit 2	Visit 3 End of Intervention		Visit 4 End of Study
	Core Baseline[1] Day -21 to 1	Non- Core Baseline[2] Day 1 to Day 21	9-month + 3 months	15-18 month + 3 months	Phone follow up[3] ± 7 days	24-month ± 28 days
Assessment						
Concomitant Med. Review[6]		X	X	X	X	X
Treatment Allocation						
Randomisation	X					
Diagnosis						
SCID5-RV (Modules A & B)	X			X		X
Intervention						
Participants in DRS+[7]						
EBIRT[8]	←	———	→	←	- - - - - →	Post intervention Follow up

[6] To maintain blinding of RAs, EBIRT clinicians will review medication adherence weekly (every second session) during the EBIRT intensive phase and every session during the EBIRT maintenance phase. EBIRT clinicians will also check concomitant medications every 6 weeks during the intervention phase (up to minimum of 15 months).

[7] Reduce antipsychotic medication dose by 25% every month for 3 months as clinically indicated.

[8] EBIRT intensive phase: Twice weekly individual therapy sessions to month 9, maintenance/monitoring phase 4-6 weeks individual therapy for a minimum of 6 months. A checklist recording details and items covered in of the EBIRT (CBT) Session will be completed every session by the Clinician and entered directly into the eCRF. The IPS Worker will also complete a checklist recording items covered in every session and enter this in to the eCRF. This data will be used to assess fidelity of EBIRT.

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Dose reduction in FEP: Study Protocol

	Visit 1 Baseline		Visit 2	Visit 3 End of Intervention		Visit 4 End of Study
	Core Baseline[1] Day -21 to 1	Non- Core Baseline[2] Day 1 to Day 21	9-month + 3 months	15-18 month + 3 months	Phone follow up[3] ± 7 days	24-month ± 28 days
Assessment						
Medication Compliance						
Clinician's compliance rating[5]		X	X	X		
MARS[5]		X	X	X		X
Medication side effects						
LUNSERS		X	X	X		X
Symptomatology						
BPRS[9]	X		X	X	X	X
SANS		X	X	X		X
DASS-21		X	X	X	X	X
CDSS		X	X	X		X
IPASE		X	X	X		X
Functioning & Quality of Life						
SOFAS[8]		X	X	X	X	X
Vocational functioning		X	X	X	X	X

[9] In addition to assessment time-points and telephone follow-up, the BPRS and SOFAS will be measured weekly during the intensive phase and at therapy sessions during the maintenance phase for purposes of discontinuation criteria.

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Dose reduction in FEP: Study Protocol

	Visit 1 Baseline		Visit 2	Visit 3 End of Intervention		Visit 4 End of Study
	Core Baseline[1] Day -21 to 1	Non- Core Baseline[2] Day 1 to Day 21	9-month + 3 months	15-18 month + 3 months	Phone follow up[3] ± 7 days	24-month ± 28 days
Assessment						
WHOQoL-BREF		X	X	X		X
ULCALS		X	X	X		X
MHCS		X	X	X		X
The Self-efficacy Scale		X	X	X		X
BPNS		X	X	X		X
Daily functioning and affect						
SEMA[10]		X	X	X		X
Pre-morbidity and Illness						
NOS		X				
Trauma						
CTQ		X				
Metabolic monitoring						
Clinical Bloods[11]		X	X	X		X

[10] SEMA will be used to deliver electronic surveys (to be administered directly after the baseline and follow up assessments (visits 1-4) at 8 time points per day in the waking hours of each participant for a period of 7 days. Only participants who have smartphones will complete these surveys.

Dose reduction in FEP: Study Protocol

	Visit 1 Baseline		Visit 2	Visit 3 End of Intervention		Visit 4 End of Study
	Core Baseline[1] Day -21 to 1	Non- Core Baseline[2] Day 1 to Day 21	9-month + 3 months	15-18 month + 3 months	Phone follow up[3] ± 7 days	24-month ± 28 days
Assessment						
Blood pressure, height, weight and waist circumference[12]		X	X	X		X
Substance Use						
AUDIT		X	X	X		X
ASSIST		X	X	X		X
Neurocognitive						
WRAT-4		X				
BACS		X	X	X		X
ER-40		X	X	X		X
The Hinting Task		X	X	X		X

[11] Clinical bloods will involve testing for fasting glucose, haemoglobin A_{1C}, fasting triglycerides and fasting total HL cholesterol.. Clinical Bloods assessment to be completed within two weeks of randomisation and within two weeks of Visits 2 to 4.

[12] Blood pressure, height, weight and waist circumference will also be measured at approximately 12, 18, and 21 months in addition to study visits. These will be measured by study RAs.

For Peer Review

Dose reduction in FEP: Study Protocol

	Visit 1 Baseline		Visit 2	Visit 3 End of Intervention		Visit 4 End of Study
	Core Baseline[1] Day -21 to 1	Non- Core Baseline[2] Day 1 to Day 21	9-month + 3 months	15-18 month + 3 months	Phone follow up[3] ± 7 days	24-month ± 28 days
Assessment						
PAL		X	X	X		X
Edinburgh Handedness Inventory		X				
NSSR		X	X	X		X
PDQ		X	X	X		X
AES		X	X	X		X
Structural and functional Imaging						
Shoulder and Hip width[13]		X				
MRI[14]		X	X	X		X

[13] Eligibility assessment for MRI scan

[14] MRI assessment to be completed within two weeks of randomisation and within two weeks of Visits 2 to 4.

For Peer Review

Dose reduction in FEP: Study Protocol

Table 2Temporary Pause from DRS+

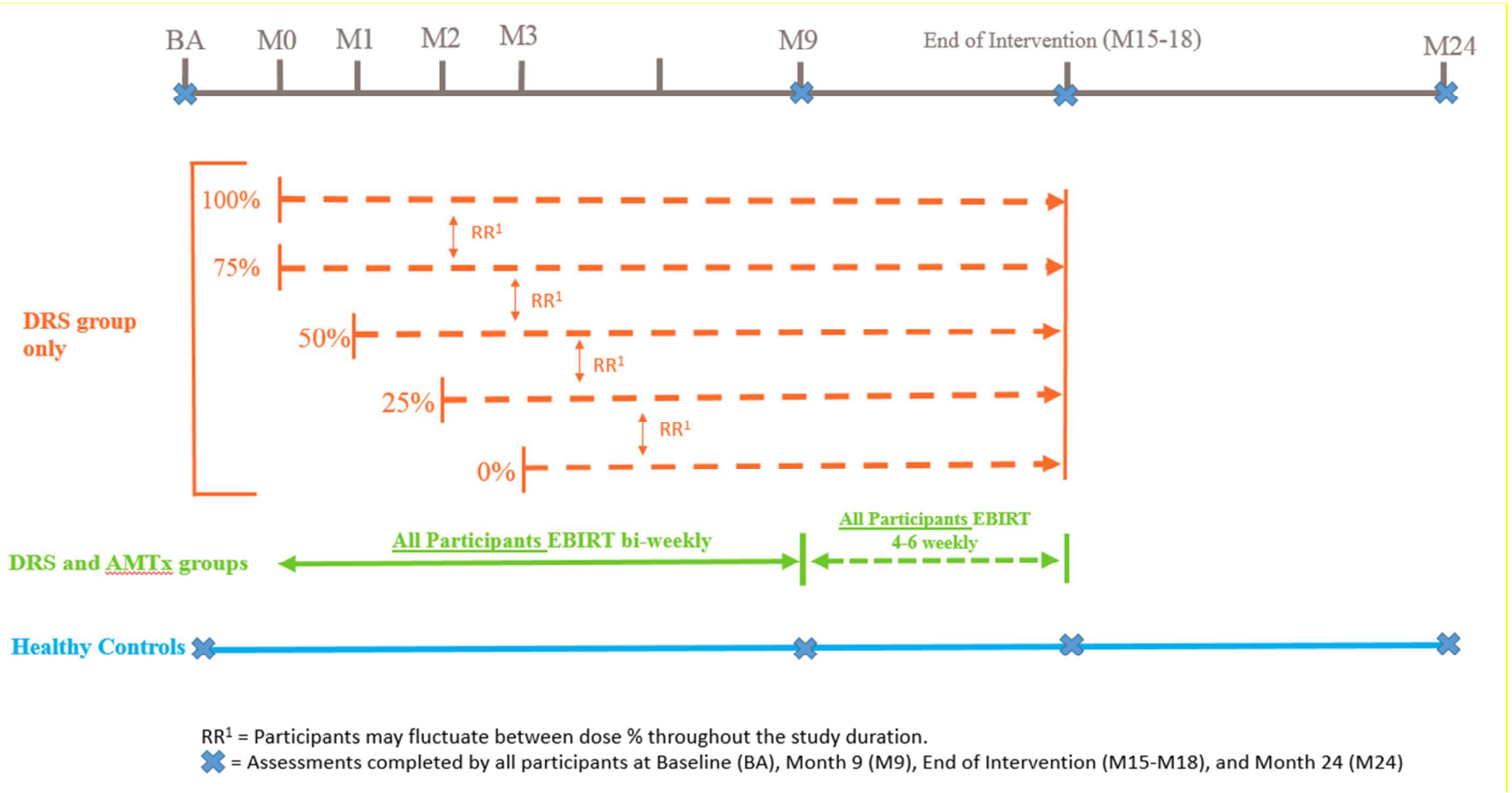
1.	Increases from 3 (mild) or below to ratings of 6 or 7 (severe or very severe) on any one of the following 3 BPRS[49] items: (i) unusual thought content, (ii) hallucinations, and (iii) conceptual disorganisation, with a duration criterion of 1 week;
2.	Significant psychotic exacerbations defined by an increase from 3 or below (for at least 1 month) on all the BPRS[49] 3 scales followed by a score of 5 (moderate) on any of the 3-items plus a 2-point increase on one of the other scales (again with the addition of a duration criterion of 1 week) or a rating of 5 on any one of the 3 scales for at least 1 month.
3.	An increase in suicidality as defined by a score of 5 or more on the BPRS[49] Suicidality subscale (i.e., many fantasies about suicide, specific suicide plan, non-lethal attempt) for a duration of at least 1 week.
AND	
4.	A significant decrease in overall functioning as defined by a 20-point drop in SOFAS score from the baseline score, maintained for one month.
OR	
5.	If the above criteria are not met but the participant is considered by their treating clinical team to have significantly deteriorated in relation to psychotic symptoms compared to baseline, and clinical response is deemed necessary, they may also be temporarily paused from the DRS+.

Table 3

For Peer Review

Dose reduction in FEP: Study Protocol

Reduce Intervention Timeline



RR[1] = Participants may fluctuate between dose % throughout the study duration.

✖ = Assessments completed by all participants at Baseline (BA), Month 9 (M9), End of Intervention (M15-M18), and Month 24 (M24)