Psychological and Psychosocial Interventions for Negative Symptoms in First Episode Psychosis: The impact of Specialized Early Intervention

Danyael Lutgens

Department of Psychiatry

Faculty of Medicine

McGill University, Montreal

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Supervisor: Dr. Ashok Malla

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Contributions

Peer reviewed Articles

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Contributions of authors:
Drs. Malla, Lepage and Manchanda had initially conceived of the project and oversaw the investigation. I conducted the analyses and wrote the first and subsequent drafts of the manuscript under the supervision of Dr. Malla, my primary supervisor. All authors contributed to revisions of the manuscript.

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Under Dr. Malla's supervision I designed this review and analysis with advice from the supervisory committee. I undertook all research, qualitative analysis and also wrote the first and subsequent drafts of the manuscript. Dr. Gariepy advised on the project and helped in conducting the quantitative analyses. Dr. Malla provided supervision of all the drafts of the manuscript and the analyses. All authors contributed to revisions of the manuscript.

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Contributions of authors:
As principal investigator of the large RCT of extended early intervention vs regular care, AM conceived and initiated the study, in collaboration with RJ and other co-investigators. I was involved in refining the protocol and contributed critically to all ongoing RCT meetings and procedure. I was trained to conduct clinical, including negative symptom assessments and followed 22 -24 clients. I wrote the first and subsequent drafts of the protocol manuscript under Dr. Malla's supervision. All authors contributed to revisions of the manuscript.

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I conceived of the focus and contributed to the formulation of hypothesis related to negative symptoms within the RCT. With Dr. Mallas's supervision I designed this analysis which was further modified with feedback from the thesis committee. I undertook all statistical analyses and wrote the first and subsequent drafts of the manuscript. Sherezad Abadi managed all recruitment. I was trained to perform the clinical assessments including negative symptom assessments. All authors contributed to initial protocol and to revisions of the manuscript.

Other Publications and contributions

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Non peer reviewed article

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Published Abstracts

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A personal statement

When I first came to the Prevention and Early Intervention Program for Psychosis (PEPP-Montreal) as part of my master's clinical internship, I was very eager to understand psychotic illness, not just from the perspective of scientific papers and meetings overheard but from real-life interactions. I followed several case managers as they met with clients. One case manager in particular, allowed me to come with him to visit clients in their homes and as he worked to help them to attain services that they needed in the city. Through this process, one of the aspects of illness that fascinated me was the concept of negative symptoms. With some clients, I had difficulty in reading their emotions – why were they so challenging to read? For others, it was learning that they were not eating enough because they had very little access to food, but also no motivation to find work. Some clients seemed to do no more than play video games at home every day. Was it really these individuals didn't want a job, or were there other issues going on that they were not talking about? When I asked clinicians about negative symptoms, the response was very pessimistic and few therapies were noted as being effective. Shortly after I joined PEPP- Montreal as a graduate student interested in working on negative symptoms, as a start up to my interest in negative symptoms, my supervisor offered me an opportunity to work on a small study where psychiatrists were asked about their current knowledge and perspectives of negative symptoms and their treatment. I analyzed these data and put it together as a manuscript (Chapter 2). My analysis and interpretation of these findings was the catalyst for my interest in better understanding what kinds of psychological and or psychosocial treatments might be effective. This helped me to develop my thesis and pursue the steps that form the contents of my thesis.

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ABSTRACT

Background

Negative symptoms that include blunted affect, low motivation, social withdrawal and poverty of speech have long been recognized as the hallmark of schizophrenia spectrum and psychotic disorders. Up to 27% of first episode psychosis (FEP) and a larger portion of chronic patients show negative symptoms that are not the result of depression, positive symptoms such as delusions or hallucinations, or medication side effects (Hovington et al. 2012; Malla et al. 2002). Negative symptoms are highly associated with poor functioning, including the ability to engage independently in daily life activities and to have meaningful social relationships. As such, negative symptoms contribute to caregiver burden and to the social cost of disability (Davies and Drummond 1994; Goetzel et al. 2004). Since 2005, an absence or a mild level of negative symptoms have been considered a requirement for the rating of remission in schizophrenia (Andreasen et al. 2005).

Despite the impact of negative symptoms on outcomes, it has long remained unknown as to how psychiatrists who regularly treat negative symptoms of psychosis perceive such symptoms and the effectiveness of available interventions. Indeed, there are a paucity of effective treatments available (Fusar-Poli et al. 2014; Kirkpatrick et al. 2006). Antipsychotics that are effective for positive symptoms show little or, at best, limited effect on negative symptoms (Kirkpatrick et al. 2006). Other biological treatments such as repetitive transcranial magnetic stimulation (rTMS)(Hovington et al. 2013) and antidepressant medication (Fusar-Poli et al. 2014) similarly demonstrate little evidence for their effectiveness. Instead, the National Clinical Institute of Clinical Excellence (NICE) guidelines suggest using psychological and psychosocial therapies as an add-on treatment (Health and Excellence 2009). While there is some evidence for their utilization with negative symptoms, reviews have either been limited in scope or have suffered

from poor methodology. For example, Fusar-Poli and colleagues investigated a range of biological and non-biological treatments for negative symptoms in their meta-analysis but did not differentiate and lumped all psychological and psychosocial interventions into a single effect size, while omitting many studies (Fusar-Poli et al. 2014). Another meta-analysis investigated psychological interventions in schizophrenia but their primary outcome was positive symptoms and many models of treatment were similarly missed (Turner et al. 2014). Finally, a systematic review that investigated psychological and psychosocial interventions for negative symptoms failed to follow methodological guidelines and again overlooked several categories of intervention (ex. dance, music, specialized early intervention) (Elis, Caponigro, and Kring 2013). A rigorous meta-analysis and systematic review of high quality trials comparing a broad range of available non-biological interventions with negative symptoms as the primary outcome of interest had not been conducted up until recently (see Chapter #2).

Conversely, there is evidence of significant negative symptom improvements in first episode psychosis when patients are treated in a specialized early intervention service (EI) (see Chapter #2). However, it is unclear whether the improvement is sustained beyond the initial two years of EI, once patients are transferred to regular care (Bertelsen et al. 2008). Given the first few years following a FEP represent a 'critical period' of intervention for securing long-term trajectories, it is important to examine the progress of negative symptoms and whether after the usual two years in an EI service, any further progress is likely to occur with extended EI compared to regular care.

A recent Danish RCT reported no significant effect of extending EI from 2 to 5 years; however, they assessed patients at only two time points: at the end of two years and then three years later.

This study also did not report how negative symptoms progressed during the initial 2 years of EI treatment. This thesis is based on data from a Canadian RCT that similarly examined the optimal duration of treatment, but with regular multiple assessment points. The trajectory of negative symptoms within this FEP cohort is examined both over the 1st 2 years of EI and following transfer to either extended EI for an additional 3-years or regular care.

Purpose

The objectives of this thesis were to: A) investigate how psychiatrists who regularly treat negative symptoms in psychosis perceive such symptoms and whether they find any available treatments to be more or less effective; B) conduct a systematic review and meta-analysis on the effectiveness of available psychological and psychosocial interventions to treat negative symptoms in psychosis; C) to present a protocol for an RCT to determine the optimal period of EI for negative symptoms in FEP; D) to examine the longitudinal course of negative symptoms and its dimensions in FEP over the first 2 year period of EI and; E) to investigate whether further gains in negative symptoms can be achieved over the subsequent 3-years with any differential benefit of extended EI vs. regular care

Methods

First, Canadian Psychiatrists were randomly contacted for an online or in paper survey, using the Canadian Medical Directory. Survey questions included how often they observed patients with psychosis to have negative symptoms as well as their perception as to the kinds of treatments available and their effectiveness. Second, a systematic review and meta-analysis of all non-biological interventions for negative symptoms in psychosis was undertaken. Third, evidence was evaluated to suggest that the optimal length of EI in FEP remains a critical clinical and research gap. Hence, a protocol was designed for an RCT with remission as the primary, and negative symptoms, as a secondary outcome. Finally, FEP patients who received

2 years of EI from the Prevention and Early Intervention Program for Psychosis (PEPP-Montreal) were randomized to either regular care or extended EI for an additional 3-years for the entire hypothesized 5 year critical period in FEP.

Total negative symptom ratings as well as negative symptom dimensions were available over 22 time points. For the first 2 years of EI assessments were conducted from baseline and over months 1, 2, 3, 6,9, 18 and 24. Post randomization assessments were conducted every 3-months for the subsequent 3 years or until the patient dropped out of the study.

Results

For the first survey, 206 Canadian psychiatrists responded. A majority (80%) indicated a high prevalence of persistent negative symptoms in patients with schizophrenia. Juxtaposed to this was a majority of psychiatrists (83%) reporting that available treatments were not seen as effective. Within the systematic review and meta-analysis (Manuscript 1), ninety-five RCT studies of either psychological or psychosocial interventions, 72 with complete quantitative data, were obtained that reported negative symptom outcomes. We found mild to moderate effectiveness for CBT, skills based, exercise and music treatments. There was significant support for EI models in FEP. The overall quality of RCTs was moderate, with high levels of heterogeneity that was less evident in RCTs of EI. From the protocol (Manuscript 2), we found that evidence for sustaining long-term improvement by extending EI past the first 2 years of FEP was equivocal, warranting a high quality RCT to investigate the optimal duration of treatment for overall remission, including negative symptom outcomes. Results of the final study (Manuscript 3) suggest that negative symptoms in FEP improve significantly over the first 2 years of EI with a different trajectory for the domain of motivation that remits early but then stabilizes around month 9, compared to the domain of expressivity that continues to improve through month 24 (with a plateau between months 3-18). We found negative symptoms to improve past the 3rd year before stabilizing,with no difference regarding patients randomized to regular care or extended EI. Further negative symptom improvements seen up to 15-months post randomization reflect changes expressivity but not in motivation that leveled before the end of the first 1-year of EI.

Conclusions and significance

While psychological and psychosocial interventions may be utilized effectively to treat negative symptoms in psychosis, the extent of their impact is restricted to mild and moderate outcomes. Evidence that EI delivered in FEP significantly reduces negative symptoms supports the application of an assertive model of care, in which several psychological and psychosocial interventions are provided, delivered early in the course of illness. That negative symptoms in FEP show a limited window of improvement (between 1-9 months for motivational deficits and between 1-15 months for deficits in expressivity), further highlights the importance of the earliest intervention. As negative symptoms continue to decrease post randomization equally within the extended EI and regular care, this suggests that intensive, integrative and phase specific treatment delivered early, over the 1st 2 years of FEP, is sufficient to maintain long-term improvements and to also produce additional post treatment gains. Future studies may benefit from determining whether negative symptom trajectories vary among patient subgroups and whether treatments and services better aimed at increasing motivation will further improve long-term negative symptom outcomes.

RÉSUMÉ

Interventions psychologiques et psychosociales pour les symptômes négatifs en premier épisode psychotique.

Contexte

Des symptômes négatifs qui incluent l'affectivité diminuée, la basse motivation, le retrait social et le language pauvre ont longtemps été reconnus comme la marque du spectre schizophrénique et des troubles psychotiques. Jusqu'à 27% de premier épisode psychotique (PEP) et une plus grande proportion de patients chroniques démontrent des symptômes négatifs qui ne sont pas le résultat de la dépression, de symptômes positifs tels que le délire ou les hallucinations, ou les effets secondaires de la médication (Hovington et al. 2012; Malla et al. 2002). Les symptômes négatifs sont hautement associés au mauvais fonctionnement, incluant l'abilité de s'engager indépendamment dans les activités de vie quotidienne et d'avoir des relations sociales significatives. Ainsi, les symptômes négatifs contribuent au fardeau des intervenants et au coût social des troubles et handicaps (Davies and Drummond 1994; Goetzel et al. 2004). Depuis 2005, une absence ou un faible niveau de symptômes négatifs sont considérés une exigence pour le taux de rémission de schizophrénie (Andreasen et al., 2005).

Malgré l'impact des symptômes négatifs sur les résultats, il y a un manque de traitements effectifs disponibles (Fusar-Poli et al. 2014; Kirkpatrick et al. 2006). Les antipsychotiques qui sont effectifs pour les symptômes positifs montrent peu, ou au mieux un effet limité sur les symptômes négatifs. D'autres traitements biologiques tel que la stimulation magnétique transcraniale répétitive (rTMS) (Hovington et al. 2013) et les médicaments antidépresseurs (Fusar-Poli et al. 2014) (Paolo Fusar-Poli et al., 2014) montrent de façon similaire peu de

preuves de leur efficacité. À la place, les directives du National Clinical Institute of Clinical Excellence (NICE) suggèrent d'utiliser les thérapies psychologiques et psychosociales comme traitement complémentaire (N. I. f. Health & Excellence, 2009). Alors qu'il y a des indications en faveur de leur utilisation pour les symptômes négatifs, les analyses ont soit été limitées dans leur étendue ou ont souffert d'une piètre méthodologie. Par example, Fusar-Poli et collègues ont examiné une variété de traitements biologiques et non-biologiques des symptômes négatifs dans leur méta-analyse mais n'ont fait aucune différentiation et ont regroupé toutes les interventions psycologiques et psychosociales en un effet de taille unique, tout en omettant plusieurs études (Paolo Fusar-Poli et al., 2014). Une autre méta-analyse a analysé les interventions psychologiques en schizophrénie mais le résultat principal était que les symptômes positifs et plusieurs modèles de traitement n'avaient également pas été relevés (Turner, van der Gaag, Karyotaki, & Cuijpers, 2014). Finalement, une révision systématique qui enquêtait les interventions pour les symptômes négatifs a échoué à suivre la méthodologie et a encore une fois négligé plusieurs catégories d'intervention (dance, musique, intervention précoce spécialisée) (Elis, Caponigro, & Kring, 2013). Une méta-analyse rigoureuse et une révision systématique d'essais clinique de haute qualité comparant un large spectre d'interventions non-biologiques disponibles avec les symptômes négatifs comme première source d'intérêt n'a pas été menée jusqu'à récemment (voir Chapitre#2).

À l'opposé, il existe des preuves d'améliorations significatives des symptômes négatifs en premier épisode psychotique quand les patients sont traités par un service d'intervention précoce spécialisé (IP) (voir Chapitre #2). Cependant, il n'est pas clair si les améliorations durent au-delà des deux premières années de l'IP, une fois que les patients sont transférrés aux soins réguliers (Bertelsen et al., 2008). Considérant que les premières années suivant un PEP représentent une

'période critique' d'intervention afin d'assurer une trajectoire à long terme, il est important d'examiner le progrès des symptômes négatifs suivant les deux premières années habituelles et de déterminer s'il y a un progrès supplémentaire probable dû à l'IP prolongée en comparaison aux soins réguliers.

Un ECR Danois récent rapportait qu'il n'y avait pas d'effet significatif d'étendre l'IP de 2 à 5 ans; toutefois, ils n'ont évalué les patients qu'à deux moments: à la fin de deux années et ensuite trois ans plus tard. L'étude a aussi omis de rapporter si les symptômes négatifs progressaient durant les 2 années initiales du traitement d'IP. Cette thèse est basé sur les données d'un ECR Canadien qui a semblablement examiné la durée optimale de traitement mais avec des temps d'évaluation multiples et réguliers. La trajectoire des symptômes négatifs à l'intérieur de cette cohorte d'ECR est examinée au cours des 2 premières années d'IP et suivant le transfert à soit une IP prolongée de 3 années additionnelles ou aux soins réguliers.

Objectif

Les objectifs de cette thèse étaient de: A) mener une révision systématique et une méta-analyse de l'efficacité des interventions psychologiques et psychosociales dans le traitement des symptômes négatifs de la psychose B) présenter un protocol pour qu'un ECR puisse déterminer la période optimale d'IP pour les symptômes négatifs du PEP; C) examiner le cours longitudinal des symptômes négatifs et ses dimentions en PEP durant la première période de 2 années et D) évaluer s'il y a d'autre gains à obtenir pour les symptômes négatifs au cours des 3 années suivantes avec des bénéfices différentiels pour l'IP prolongée vs. les soins réguliers.

Méthodes

Premièrement, une révision systématique et une méta-analyse de toutes les interventions non-biologiques pour les symptômes négatifs en psychoses a été menée. Deuxièmement, les preuves évaluées suggèrent que la durée optimale d'IP en PEP demeure un inconnu critique en pratique et en recherche. Par conséquent, un protocol a été conçu pour un ECR avec la rémission en tant que résultat primaire et les symptômes négatifs en résultats secondaires. Troisièmement, les patients en PEP qui ont reçus 2 ans d'IP du Prevention and Early Intervention Program for Psychosis (PEPP-Montreal) ont été randomizés soit au soins réguliers ou à une IP prolongée de 3 années additionnelles pour l'entièreté d'une période critique de 5 ans supposés en PEP. L'entièreté des évaluations des symptômes négatifs ainsi que les dimensions des symptômes négatifs étaient disponibles sur la totalité de 22 points. Pour les deux première années d'IP, les évaluations étaient menées du début et au cours des mois 1, 2, 3, 6, 9, 18 et 24. Des évaluations post-randomisation ont été menées tous les 3 mois pour les 3 années subséquentes ou jusqu'à ce que le patient se retire de l'étude.

Résultats

Pour la révision systématique et la méta-analyse (Manuscrit 1), quatre-vingt-quinze études ECR d'interventions psychologiques ou psychosociales, 72 avec données quantitatives complètes, ont été obtenues qui rapportait avoir eu des symptômes négatifs. Nous avons trouvé une efficacité modérée pour la TCC, et les traitements basés sur les habiletés, l'exercise et la musique. Il y avait des données significatives pour les modèles d'IP en PEP. La qualité d'ensemble des ECR était modérée, avec de haut niveaux d'hétérogénéité moins évidents en ECR d'IP. Du protocol (Manuscrit 2), nous avons trouvé que les preuves du maintien d'améliorations à long terme en prolongeant l'IP au-delà des 3 premières années de PEP étaient équivoques, justifiant qu'un ECR

de haute qualité enquête la durée optimale de traitement pour le taux de rémission global, incluant les symptômes négatifs. Les résultats de l'étude finale (Manuscrit 3) suggèrent que les symptômes négatifs en PEP s'améliorent significativement lors des 2 premières années d'IP avec une trajectoire différente pour le domaine de la motivation qui montre des progrès tôt mais qui ensuite se stabilize vers le mois 9, comparé au domaine de l'expressivité qui continue de s'améliorer jusqu'au mois 24 (avec un plateau entre les mois 3-18). Nous avons trouvé que les symptômes négatifs s'amélioraient au-delà de la 3ème année avant de se stabiliser, sans aucune différence entre les patients randomizés aux soins réguliers ou à une IP prolongée. Des symptômes négatifs supplémentaires observés jusqu'à 15 mois de post-randomisation reflètent des changements d'expressivité mais pas de motivation qui se nivellaient avant la fin de la première année d'IP.

Conclusions et implications

Bien que les interventions psychologiques et psychosociales peuvent être utilisées efficacement pour traiter les symtpômes négatifs de la psychose, l'étendue de leur impact est limitée à des résultats légers à modérés. Les preuves que les IP appliquées en PEP réduisent significativement les symptômes négatifs soutiennent l'application d'un model rigoureux de soins, dans lequel plusieurs interventions psychologiques et psychosociales sont fournies tôt dans la maladie. Le fait que les symptômes négatifs en PEP montrent une fenêtre limitée d'amélioration (entre 1-9 mois pour les déficits motivationels et entre 1-15 mois pour les déficits d'expression), souligne d'autant plus l'importance d'une intervention au stage le plus précoce. Puisque les symptômes négatifs continuent de décroître également entre les IP prolongées et les soins réguliers, cela suggère que les traitements de phase spécifique intensifs et intégratifs fournis tôt lors du premier

2 ans de PEP sont suffisants pour maintenir des améliorations à long-terme et aussi pour produire des gains additionels post-traitement. Il peut être bénéfique aux études ultérieures de déterminer si les trajectoires de symptômes négatifs varient entre les sous-groupes de patients et si les traitements et services visant à accroître la motivation peuvent améliorer d'avantage les résultats à long-terme sur l'apparition des symptômes négatifs.

ABBREVIATIONS

BPRS: Brief Psychiatric Rating Scale

CAINS: The Clinical Assessment Instrument for Negative Symptoms

CATEGO: Categorie (French)

CBT: Cognitive Behavioural Therapy

CI: Confidence Interval

COAST: Croydon Early Intervention Team – Specialized Early Intervention Program in South London

CORS: Circumstances of Onset and Relapse Schedule

DUP: Duration of Untreated Psychosis

DSM IV: Diagnostic and Statistical Manual of Mental Disorders, 4th ed.

EI: Specialized Early Intervention Service

FEP: First Episode Psychosis

GAF: Global Assessment of Functioning (split version, function)

ICD-9/10: The International Classification of Diseases – 9/10

IAROS: Interview for the retrospective onset of schizophrenia

LEO: The Lambeth Early Onset trial

NIMH: National Institute for Mental Health (US)

NIH: National Institute of Health

OPUS: Specialized early intervention program in Denmark, - not an abbreviation

PANSS: Positive and Negative Symptom Scale

PAS: Premorbid Adjustment Scale

PEPP: Prevention and Early Intervention Program for Psychosis

PNS: Persistent Negative Symptoms

QOL: Quality Of Life"

RAISE: Recovery after an Initial Schizophrenia Episode – A specialized Early Intervention Program in the US

RCT: Randomized Clinical Trial

RR: Relative Risk

SANS: Schedule for Assessment of Negative symptoms in Schizophrenia

SAPS: Schedule for Assessment of Positive symptoms in Schizophrenia

SEI: Specialized Early Intervention

SGA: Second Generation Antipsychotics

SOFAS: Social and Occupational Functioning Scale

SST: Social Skills Training

TAU: Treatment AS Usual

QLS: Quality of Life Scale

Chapter 1: General Introduction

1.1 Schizophrenia spectrum and psychotic disorders

1.1.1 General Symptoms

Schizophrenia spectrum and related psychotic disorders are defined by severe phenomenological and behavioural disturbance. Current diagnoses of schizophrenia and other psychotic disorders are anchored onto 2 clusters of positive and negative symptoms (Liddle 1987; Malla et al. 1993; Kay, Flszbein, and Opfer 1987). Positive symptoms are considered those that are superimposed onto the range of normal behaviour, and include delusions and hallucinations, but also disorganized thinking. Conversely, negative symptoms that are the focus of this thesis and that will be covered in more detail, are conceptualized as a loss, restriction, or diminished range of normal functional behaviours.

1.1.2 Basis for Diagnoses

Utilizing these 2 dimensions of symptoms, but requiring the presence of positive symptoms not better explained by a mood disorder, impeding normal functioning, several diagnoses under the umbrella of Schizophrenia Spectrum Disorders are possible. Diagnostic definitions are based almost exclusively on observed symptomology, illness pathways, and effects of medications (Tandon, Nasrallah, and Keshavan 2010; Andreasen 2006). Differing diagnoses are largely determined by duration (ex. Brief Psychotic Disorder or Schizophreniform); etiology (ex. Drug Induced, Substance/Medication – Induced, Due to Another Medical Condition); corresponding symptomology (ex. Schizoaffective); and severity (ex. Schizophrenia). The term First Episode

Psychosis is largely used to refer to those that are in early in the course of illness and treatment rather than a specific diagnosis.

1.1.3 Co-morbid mental disorders

A substantial percentage of those diagnosed under the Spectrum of Schizophrenia will also struggle at some point with one or more co-morbid mental disorder diagnoses including: depression (50%), substance abuse (47%), post traumatic stress disorder (29%), panic disorder (23%), obsessive-compulsive disorder (15%) (Buckley et al. 2008) and social phobia (11%) (Achim et al. 2009). While co-occurring disorders are likely to impact treatment outcomes and functioning, their comparably high prevalence among such populations suggests they are reflective of underlying pathology, although the possibility of random association has not been ruled out (Cuesta et al. 2009).

1.2 Epidemiology of schizophrenia spectrum and psychotic disorders

1.2.1 Distribution

Globally, there are varying estimates as to the annual incidence of schizophrenia from 7 – 40/ 100,00/year depending on the use of narrow vs. broad clinical definitions and measures (ex. ICD-9; CATEGO class S) (Organization 1978; Sartorius et al. 1986; Wing, Cooper, and Sartorius 1974). It is estimated that the average annual incidence of schizophrenia is 15 per 100,000 (Tandon, Keshavan, and Nasrallah 2008). At any given time, the point prevalence of

schizophrenia is approximately 1.4 to 4.56 cases in a population of 1000 (Tandon, Keshavan, and Nasrallah 2008; Jablensky 2000). There is evidence that the world-wide prevalence has increased by 19% between 2005-2015 (Vos et al. 2016; Murray and Lopez 1997), although whether this is a by-product of increased awareness of mental illness or reflective of underlying incidence is unknown (Okkels et al. 2013; Chan et al. 2015). The median life-time a median lifetime prevalence of a diagnosis of schizophrenia is 4.0 (McGrath et al. 2008). A systematic review of 200 studies corroborates this finding (Saha et al. 2005). World-wide, the mean lifetime risk of developing schizophrenia is 7 percent (out of 1000) (McGrath et al. 2008; Saha et al. 2005).

It is generally agreed that males compared to females have a higher likelihood of developing schizophrenia with an increased relative risk of approximately 1.4 (McGrath et al. 2004) to 2.3 (Kirkbride et al. 2006). Onset of schizophrenia occurs early and is younger for males (within early to late adolescence) than females (within early to mid adulthood) (ex. (Loranger 1984; Goldstein, Tsuang, and Faraone 1989; Häfner et al. 1994; Castle, Sham, and Murray 1998; Van Der Werf et al. 2014). The the greatest incidence of schizophrenia occurs between the ages of 18 – 25 for males. A study conducted in Montreal, Canada finds the annual average incidence to be 82.9 per 100 000 for males compared to 32.2 per 100 000 per females (Anderson et al. 2012). For females, there are likely to be 2 incidence peaks with the first between the ages of 25-35 and the second after the age of 40 (Van Der Werf et al. 2014; Häfner et al. 1994; Castle, Sham, and Murray 1998). However, data from a meta-analysis contends that the difference in age onset between sexes has been overestimated (Rajji, Ismail, and Mulsant 2009).

Minor cross-cultural variation in rates of schizophrenia incidence are argued to stem from measurement discrepancy (Jablensky 2000). However, relatively large intra-population differences in rates of schizophrenia incidence cross-culturally are much more likely to be systemic (Kirkbride et al. 2008), reflecting social inequality and depravation (Kirkbride et al. 2012). For example, a study conducted in Montreal, Canada reported that incidence of schizophrenia was significantly higher within the most materially deprived (RR 1.75; 95% CI 1.33 to 2.30) and the most socially deprived (RR 1.84; 95% CI 1.28 to 2.64) neighborhoods in the city (Anderson et al. 2012). Similarly, a systematic review suggests a higher relative risk of psychotic disorders (between 2 and 3) among both first but also second generation immigrants that was higher for those with visible minority status, suggesting a critical role of social discrimination (Bourque, van der Ven, and Malla 2011).

1.2.2. Determinants of risk

The genetic loading of psychotic disorders is high (80%-90%; (McGuffin et al. 1984), with a complex interplay between genes (Derks et al. 2012) that is contextually embedded (Van Os and McGuffin 2003; Crow et al. 2013). A myriad of factors including obstetric complications (Khandaker et al. 2013; Cannon, Jones, and Murray 2002; Brown 2012), season of birth (winter) (Davies et al. 2003), sex (male) (Castle and Murray 1991), urbanization (Lederbogen et al. 2011), childhood adversity (Varese et al. 2012), social inequality (Cantor-Graae and Selten 2005), and drug use (Van Os et al. 2002) are implicated temporally in the pathogenesis of psychotic disorders within a possibly multiple, additive relationship (Van Os, Rutten, and Poulton 2008).

1.3 Consequences and of schizophrenia spectrum and psychotic disorders

Psychotic disorders are associated with great suffering such as, elevated rates of suicide (Palmer, Pankratz, and Bostwick 2005), drug abuse (Dixon et al. 1991; Regier et al. 1990), and homelessness (Folsom and Jeste 2002). Due to the age of onset of such disorders, they tend to critically disrupt psychosocial development (Birchwood, Mcgorry, and Jackson 1997), often leading to a lifetime of unemployment (Mechanic, Bilder, and McAlpine 2002; Mueser, Salyers, and Mueser 2001) and disability (Organization 2001; Harwood, Sayer, and Hirschfeld 2004). Psychosis can be a powerful contributing factor to family burnout (Solomon and Draine 1995; Maurin and Boyd 1990; Rössler et al. 2005), and the social implications of psychosis are far-reaching (Whiteford et al. 2013). It is the most expensive of all psychiatric disorders world-wide, (Wyatt et al. 1995; Wu et al. 2005) with sufferers occupying 8% of hospital beds in Canada (Goeree et al. 2005), contributing towards an estimated 2.02 billion in direct and indirect costs (Goeree et al. 2005) in this country alone.

1.4 Negative symptoms

1.4.1 A short introduction to negative symptoms

Negative symptoms (ex. Diminished affect, motivational deficits) are not unique to schizophrenia and can be found in varying degrees across a range of medical and other psychiatric disorders (Harciarek et al. 2013). In their pioneering descriptions of schizophrenia in the early part of the 20th century, both Kraeplin (1904, 1981) and Bleuler (1950, 1911), gave prime importance to negative symptoms as part of the underlying pathology in psychotic disorders, critically associated with a worse prognosis (Kraepelin 1919; Malaspina et al. 2014). Kraeplin, in 1904 characterized dementia praecox as "The complete loss of mental activity, and of interest in particular, and the failure of every impulse to energy, are such characteristic and fundamental indication that they give a very definite stamp to the condition" (McNally 2016; Kraepelin 1904).

1.4.2 Separating and identifying negative symptoms

1.4.2.1 Historical trends

The positive-negative symptom dichotomy in general that diagnoses of psychotic disorders have adopted, is largely attributed to the early works of Jackson (1875), who conceptualized a hierarchical model of the nervous system to explain epilepsy. In fact, evidence suggests that this distinction within epilepsy occurred even earlier with Reynolds (1857), albeit within a more simplistic epistemology (Berrios, Luque, and Villagrán 2003).

However, it was the French psychiatrists, de Clerambault (published posthumously, 1942) and later Ey (1962) who transferred the positive-negative terminology from medicine into psychiatry (Malaspina et al. 2014). Despite this early emphasis on negative symptoms, the discovery of antipsychotic medications to treat positive symptoms in the 1950s initiated a determined shift towards clinical and research concentration on Schneiderian first rank symptoms exclusively (Mellor 1970). This paradigm remained unchallenged until the 1980's (Crow 1980). Crow, utilizing brain scans of patients and through post mortem studies considered 2 variants of schizophrenia. The first type was categorized as acute, responsive to antipsychotic medications targeting dopamine transmitters, and reversible in course. The second type was likely to be chronic, paralleled by cognitive difficulties and negative symptoms including: affective flattening, poverty of speech, loss of drive. This second type was observed to be unaffected by antipsychotics (Crow 1980). While the types might overlap, the presence of symptoms relating to type two schizophrenia indicated a more severe course (Crow 1980).

Closely following on the heels of Crow's publication, Andreason introduced a rating scale for measuring negative symptoms (Andreasen 1982). Most recently, and in light of emerging evidence of the pervasiveness of negative symptoms as an "unmet therapeutic need" with critical implications for outcomes in schizophrenia, consensus criteria for remission in schizophrenia now includes a rating of mild or less on negative, as well as on positive, symptom scales (Andreasen et al. 2005). Negative symptoms are once again in the spotlight.

1.4.2.2 Contemporary negative symptom conceptualization and measurement

Statistical modelling of schizophrenia confirm that negative symptoms constitute a key and separate factor from positive symptoms and cognitive deficits (Emsley et al. 2003; Salokangas 1997; Blanchard and Cohen 2005). Scales developed to measure negative symptoms in schizophrenia include: The Brief Psychiatric Rating Scale (BPRS) with 4 items for negative symptoms (Overall and Gorham 1962); The Krawiecka-Manchester Scale (Krawiecka, Goldberg, and Vaughan 1977) with 13 items; The Emotional Blunting Scale with 16 items (Abrams and Taylor 1978); The Scale for the Assessment of Negative symptoms (SANS) with 20 items not including attention (Andreasen 1982); The Negative Symptom Scale of Pogue – Geile and Harrow with 12 items (Pogue-Geile and Harrow 1985); The Positive and Negative Symptom Scale – Negative Symptom Subscale (PANSS) with 7 items (Kay, Flszbein, and Opfer 1987); The Negative Symptom Assessment (NSA-16) with a 16 (Axelrod, Goldman, and Alphs 1993) and 4 item version (Alphs et al. 2010), The Brief Negative Symptom Scale with 13 items (BNSS) (Kirkpatrick et al. 2010; Strauss et al. 2012), and the Clinical Assessment Interview for Negative Symptoms (CAINS) (Horan et al. 2011; Kring et al. 2013).

Overall, the SANS is considered to be one of the most widely used and complete negative symptom scales in psychosis (Kirkpatrick et al. 2006). Both the BNSS and the CAINS were designed following the NIMH MATRICS consensus definition and distinguish among components of pleasure, motivation, and sociality, often missing from other instruments (Strauss and Gold 2016; Marder and Galderisi 2017). The PANSS and the BPRS meanwhile include items of positive symptoms including overall psychopathology, not included in other instruments, and has been utilized most often in clinical trials with antipsychotic medications (ex.(Swartz et al. 2003). Other scales for negative symptoms are also available including those

with application outside of psychotic disorders (ex. (Marin, Biedrzycki, and Firinciogullari 1991). There is evidence to suggest that inter-rater reliability is more difficult to achieve with negative, compared to positive symptoms (Norman et al. 2000; Norman et al. 1996), although overall these scales show strong inter-correlation and demonstrate acceptable inter-rater reliability and validity (ex.(Norman et al. 2000; Norman et al. 1996).

Investigations of negative-symptoms-constructs suggest some overlap in measurement of negative symptoms with disorganization items on the most widely used PANSS (Kay, Flszbein, and Opfer 1987) and SANS (ex.(Sayers, Curran, and Mueser 1996) as well as with depressive and disorganization items on the BPRS (Overall and Gorham 1962). An NIH consensus report supports the following negative signs and symptom criteria: blunted affect, alogia, anhedonia, avolition, and asociality (see Table 1 (appendix 1) for breakdown of negative items and their clinical manifestations) but without items of inappropriate affect (under blunted affect) and poverty of content of speech (under alogia) that are traditionally included within measures but that also load more on disorganization (Buchanan and Carpenter 1994; McAdams et al. 1997; Peralta and Cuesta 1999; Kulhara and Avasthi 2003).

Factor analytic studies conducted across diverse schizophrenia populations and using varying negative symptom instruments (Malla et al. 2004; Malla et al. 2002; Stiekema et al. 2016; Liemburg et al. 2013; Fervaha et al. 2013), suggest a more parsimonious model of negative symptoms with better utility for prediction of outcomes. Such a model would contain only two domains with items representing amotivation and expressive deficits. Amotivation, including a lack of interest in social interactions and activities of daily living, has been linked to deficits in

anticipatory, rather than consummatory pleasure; whereby the drive to engage in events deemed to be rewarding is impaired, though the ability to enjoy rewards may still be intact (Cassidy et al. 2012; Mote et al. 2014). Expressive deficits, for their part, may be easily observed through a range of diminished intensity and frequency of facial expression, vocal inflection, gesturing, and poverty of speech (Kring and Moran 2008). Factors may overlap such that expressive deficits may be indicative of a loss of initiative or motivation (Liemburg et al. 2013) but even also of cognitive dysfunction (Green et al. 2012; Millan et al. 2014), or paranoia (Phillips et al. 1999). While both expressive and motivation deficits have been found to independently predict functioning, amotivation is more highly associated with poor outcomes, including lower levels of employment and lowered quality of output (Strauss et al. 2013). As will be discussed later however, under the section of functioning, association between functional outcome and negative symptoms should be considered in light of significant overlap between traditional measures of both (Velligan, Alphs, et al. 2009)

1.5 Negative symptom subtypes and their prevalence

Negative symptoms have diverse presentation and may be considered according to their subtypes including primary, secondary, and persistent negative symptoms (PNS). Persistent negative symptoms tend to be primary but may also be secondary with less oscillation, or a combination of both. A subset of patients may also meet the threshold for Deficit Syndrome. Such distinctions, while often challenging for clinicians to evaluate (Buchanan 2006; Lutgens et al. 2014), are critical as they may speak to differences in etiology, treatment needs and also guide

the search for effective treatments (Buchanan 2006). Primary negative symptoms are considered idiopathic and are independent of other illness processes. Secondary negative symptoms, however, may be due to introversion, paranoia (Andreasen 1990); social isolation; environmental deprivation; antipsychotic side effects including sedation and extrapyramidal symptoms; drug use; as well as depression (Carpenter Jr, Heinrichs, and Alphs 1985; Carpenter Jr and Kirkpatrick 1988; Kirkpatrick 2014) and are more likely to respond to intervention (Carpenter Jr, Heinrichs, and Alphs 1985). While different studies have adopted their own criteria for defining persistent negative symptoms (PNS), they are most often considered to: interfere with functioning; persist even during periods of clinical stability; are required to be present for any predefined period of time, although usually for a minimum of 6 months; and "represent an unmet clinical need" (Buchanan 2006; Buchanan et al. 2009; Buchanan et al. 2007). For a diagnosis of deficit syndrome, an observable presence of 2 of 6 primary negative symptoms (including: restricted affect, diminished emotional range, poverty of speech, curbing of interest, diminished sense of purpose, and diminished social drive) that remain severe for a period of at least 12 months, even during periods of clinical stability is required (Buchanan 2006; Kirkpatrick et al. 1989). Deficit syndrome is measured through the Schedule for Deficit Syndrome (Kirkpatrick et al. 1989) and must be accompanied by a diagnosis of schizophrenia.

Several studies suggest that patients with PNS, and in particular, those with deficit syndrome, constitute a unique clinical population within the schizophrenia spectrum of disorders (Kirkpatrick et al. 2001) that differ in biological correlates, risk factors and etiology (Fenton and McGlashan 1994; Strauss et al. 2008; Strauss et al. 2010). Populations with more severe negative symptoms are likely to have less positive symptoms (Sigmundsson et al. 2001), demonstrate

unique structural brain abnormalities (Koutsouleris et al. 2008; Voineskos et al. 2013; Wheeler et al. 2015; Carpenter Jr and Kirkpatrick 1988) and show a trajectory of symptomology that can be identified earlier through specific patient characteristics and symptoms (Malla et al. 2004). Those with higher levels of negative symptoms show worse long term trajectories (Strauss et al. 2008) regardless of of whether they meet the criteria for deficit syndrome (Strauss et al. 2008).

There is much evidence from high risk psychosis populations (Iyer et al. 2008a; Meyer et al. 2005; Svirskis et al. 2005; Compton, Bollini, et al. 2007) and from retrospective accounts (Tan and Ang 2001) that negative symptoms, particularly items of social isolation (Cannon et al. 1997) emerge early in the prodrome and often predate the first psychotic episode by months, if not years. Indeed, a majority of FEP patients show clinically significant negative symptoms (Malla et al. 2004; Lyne et al. 2012) and approximately 30% show primary negative symptoms not confounded by depression and/or extrapyramidal symptoms (Malla et al. 2002; Galderisi et al. 2013). At follow up, this rate is somewhat reduced, although PNS outcomes (regardless of whether they might be primary or secondary) vary from 6.7% (Galderisi et al. 2013) to 25% (Malla et al. 2004) or even higher (Hovington et al. 2011), with the variance likely dependent on the definition and criteria used (Hovington et al. 2012). Evidence from chronic schizophrenia populations suggests that up to 75 % demonstrate primary PNS (Möller et al. 2011). Taken together, findings imply a trajectory of negative symptoms that begins early and continues throughout the course of illness.

1.6 Understanding negative symptoms

1.6.1 Neuroanatomical abnormalities

Data from both chronic and FEP patients suggests underlying brain structure abnormalities, are associated with psychosis generally, and with negative symptoms specifically. In a seminal study conducted by Johnstone and colleagues (1976) utilizing computerized axel tomography (CAT), significantly increased cerebral ventricular size was found in patients with schizophrenia, compared to age matched controls (Johnstone et al. 1976). Further, within the sample of schizophrenia patients there emerged a subgroup with increased ventricular size that was significantly correlated with cognitive impairment and negative symptoms. This finding of the association between substantial lateral ventricular enlargement relative to brain volume and increased negative symptoms was shortly confirmed with other samples of patients with schizophrenia (Pearlson et al. 1984). This finding has been replicated since (Howes et al. 2009; Howes and Kapur 2009). Compared to other patient populations and controls, post mortem studies report ventricular enlargement to be particularly emphasized on the left hemisphere (Crow et al. 1989). Ventricular enlargement has also been confirmed in first episode psychosis (Steen et al. 2006), suggesting that this abnormality is independent of previous medication usage.

Juxtaposed to ventricular enlargement are overall brain volume reductions in schizophrenia (van Erp et al. 2016) and in first episode patients (Zipursky et al. 1998). Studies of cortical thickness report decreases (Goldman et al. 2009) within white (Voineskos et al. 2013) and gray matter tracts (Narr et al. 2004; Narr et al. 2005). A portion of this effect, at least in chronic patients, may be explained by long-term antipsychotic usage (Ho et al. 2011; Fusar-Poli et al. 2013). However, several studies have found that white matter as opposed to gray matter reductions in the

prefrontal cortex and in particular in the orbitofrontal sub-region (Sanfilipo et al. 2000; Voineskos et al. 2013; Hovington et al. 2015) as well as in the left hemispheric neocortical and limbic regions (Sigmundsson et al. 2001) are specifically associated with poorer socio-emotional functioning and higher levels of negative symptoms across a spectrum of patient samples. Considered overall, findings of brain alterations in psychosis suggest innate, progressive changes that may differentially impact a subset of patients with higher levels of negative symptoms (Vita et al. 2006; Haijma et al. 2012).

1.6.2 Neurotransmitter abnormalities

Increased dopamine 2 (D2) receptors in the brains of schizophrenics is a well corroborated finding and is linked to the phenomenon of positive symptoms (Seeman and Lee 1975; Owen et al. 1978; Howes and Kapur 2009). While several neurotransmitters have been linked to negative symptoms and putatively related to cognitive deficits, no causal pathways have as yet been established (Howes and Kapur 2009).

It has been hypothesized that malfunctioning dopamine transmission is similarly responsible for negative symptoms but with a reversed pattern and effect (ex.(Davis and Kahn 1991; Goldman-Rakic, Muly III, and Williams 2000; Goldman-Rakic et al. 2004). Some research has focused on dopamine D1 receptors in the prefrontal cortex, and lowered neuronal connectivity for glutamate transmission (for a review see: (Laruelle 2014).

However, a review of the literature on D1 transmission, including in drug naïve patients, reported mixed findings (Pratt et al. 2015). Notwithstanding, it has been reported that decreased synaptic dopamine function in regions of the striatum are correlated with greater levels of negative symptoms and in particular with apathy and social withdrawal, although the sample size was limited (Kegeles et al. 2010). Given the effect of antipsychotic drugs on overall dopamine suppression, studies into D1 receptors and transmission are likely to be confounded. Yet, the overall effect of dopamine antagonists and partial agonists are minimal to modest in relieving negative symptoms (Pratt et al. 2015). Schizophrenia patients with high levels of negative symptoms are less likely to be substance dependent (Volkow 2009), and laboratory inductions of dopamine using an amphetamine challenge shows decreased release compared to controls (Thompson et al. 2013). Such patterns suggest that any deficits in dopamine activity are unlikely to be re-adjusted through increasing dopamine availability (Thompson et al. 2013). Findings are complicated by the different methods used for investigation and also because of the heterogeneity of samples. That tracers utilized also bind to serotonin may further confound outcomes reported (Pratt et al. 2015).

While research into dysfunctional glutamate (excitatory transmission) has increased, this line of investigation is still in its early stages (Merritt, McGuire, and Egerton 2013; Merritt et al. 2016). Evidence from post mortem studies of reduced glutamate receptors are not conclusive (Pratt et al. 2015). While a single study reported increased glutamate in the anterior cingulate cortex (ACC) of FEP patients with heightened negative symptoms (Egerton et al. 2012; Egerton and M Stone 2012) another study reported a converse correlation (Reid et al. 2010; Poels et al. 2014).

There is some suggestion that a localized glutamate receptor (NMDA receptor) may be affected (Hammond et al. 2014), although this has not been linked to variations in symptomology, including negative symptoms (Merritt et al. 2016). Within animal models, long term injection of glutamate antagonists results in the kind of deficit and poor functioning that may be similar to negative symptoms in chronic schizophrenia (Pratt et al. 2015). In sum, while both dopamine and glutamate systems are likely involved in negative symptom expression, the process and mechanisms involved are still under investigation within various brain regions.

1.6.3 Psychosocial understanding of negative symptoms

Evidence linking childhood adversity to mental illness, including psychosis, is irrefutable (Kessler et al. 2010; Green et al. 2010; Varese et al. 2012). Most generally, it is expected that adversity, through an increased stress response, has a cascading effect on dopaminergic function, but also on cognitive schemas, that interact to increase vulnerability to mental illness (Howes and Murray 2014). Specifically, various types of childhood adversity have been empirically linked with particular content and form of positive symptom subtypes (Bentall et al. 2014), with a dose response relationship of intensity (Janssen et al. 2004).

There is little research exploring the sequelae of childhood trauma in respect to negative symptoms. However, there is some research associating cognitive schemas with negative symptoms, particularly with social behaviour and motivation. In a large sample of those with FEP, self-esteem, conceptualized as inter and intrapersonal self-respect and satisfaction, was shown to be significantly associated with PANSS negative symptoms, even when depression was

factored out (Wittorf et al. 2010). In another cross-sectional study, defeatist beliefs in patients with schizophrenia varied alongside negative symptoms (in particular low motivation) and lowered performance (Grant and Beck 2008). Findings by the same group reported that asocial beliefs in schizophrenia were associated with asocial behaviours and poor functional outcomes a year later (Grant and Beck 2008). Similarly, in two others studies with schizophrenia patients, negative appraisals and diminished effort accounted for a large portion of the variance in negative symptoms (Rector 2004; Avery, Startup, and Calabria 2009). Cognitive behavioural therapeutic interventions have leveraged this research and operate on a hypothesis that negative symptoms are the result of early life experience including repeated failure and impoverished environments that fail to reinforce motivation and social connections (Kingdon and Turkington 2005; Klingberg et al. 2011). Further, negative symptoms, such as withdrawal (including emotional withdrawal) are thought to serve as a protective mechanism in those with poor social skills, thus lessening stressors that may give rise to positive symptoms (Kingdon and Turkington 2005). Research from the social sciences in the field of motivation more generally supports this theory of decreased engagement following repeated failure and lack of opportunity (Maier and Seligman 1976). The theory of 'learned helplessness' explored empirically within psychology, suggests that for some, active retreat may provide control over an otherwise unpredictable environment (Maier and Seligman 1976; Wortman and Brehm 1975). Control over one's environment is considered a primal drive and critical for self-preservation. Other theories of negative symptom etiology that take a developmental perspective have implicated cognitive deficits, including 'theory of mind' (that will be discussed later), and its relationship to poor social skills, often reported in schizophrenia, and that are highly correlated with negative symptoms (ex. (Brüne 2005).

1.7 Negative symptom confounders and correlates

1.7.1 Cognition and negative symptoms

It has been estimated that up to 90% of chronic schizophrenia patients demonstrate impairment in at least one domain of cognitive function, with global cognitive performance an estimated one standard deviation below that of healthy controls (Palmer et al. 1997; Heinrichs 2005). Studies from FEP, however, find that only a fraction display large deviations from expected sample means (Lennertz et al. 2016). Similar to negative symptoms, cognitive impairments tend to arise early in the prodrome, predate the first psychotic episode (Nuechterlein and Dawson 1984; Green, Kern, and Heaton 2004; Lutgens et al. 2014) and remain stable over time, independent of other clinical feature such as DUP (Norman, Townsend, and Malla 2001) and positive symptoms (Rund 1998). Longitudinally, cognitive impairments, like negative symptoms, predict a range of functional outcomes (Green 1996; Green, Kern, and Heaton 2004), are resistant to available biological interventions (Marder and Fenton 2004), and likely share similar neural pathways (Karlsson et al. 2009; Labrie, Lipina, and Roder 2008). However, despite the overlap between negative symptoms and cognitive deficits, the two domains correlate only modestly and have limited association longitudinally (Friedman et al. 2002; Harvey et al. 2003; Harvey et al. 2005).

It has been suggested that negative symptoms mediate the relationship between cognition and outcome, such that cognition may imply the potential to function while negative symptoms will determine the effort applied to realize that potential (Ventura et al. 2009; Lin et al. 2013). For

example, deficits in working memory and in the ability to represent and access memory of a past pleasurable experience is likely to decrease reward anticipation, and hence motivation to apply effort for obtaining an experience (Kring and Moran 2008; Strauss and Gold 2012). The same deficits of representation and retrieval, alongside poor verbal fluency, may produce alogia, when limited cognitive stores are overstrained (Cohen, Kim, and Najolia 2013). Compromised reinforcement learning is also linked to decreased reward sensitivity that limits the desire to engage in prosocial behaviour (Gold et al. 2008). Challenges with executive functioning, including planning also correlate with negative symptoms, given the multitude of steps entailed in any educational, vocational and social pursuit (Farreny et al. 2013). Finally, poorer cognition may wear on patient's self esteem over time, negatively influencing their self perception, self-talk and thus motivation towards social and environmental interaction (Cella et al. 2014).

1.7.2 Social cognition and negative symptoms

Social cognition, while often considered alongside other indices of cognition, may reflect distinct processes with greater impact on social, as compared to other areas of functioning (Strassnig et al. 2015) including a unique association with negative symptoms (Corcoran, Mercer, and Frith 1995; Sergi et al. 2007; Couture, Granholm, and Fish 2011). Social cognition, that at its core represents the ability to have 'theory of mind' that is, the ability to infer what others may be thinking and feeling (Premack and Woodruff 1978), is often compromised in chronic schizophrenia (Sprong et al. 2007) as well as in FEP (Bora and Pantelis 2013; Bertrand et al. 2007) but is also most commonly seen in Autism spectrum disorders (Baron-Cohen 2000). Deficits in perception of non-negative, non-verbal cues have been reported in several studies

(Mandal, Pandey, and Prasad 1998; Gur et al. 2006; Lepage et al. 2011). A single study reported facial expressions of those with schizophrenia were more poorly recognized and more likely to be misidentified as neutral by the general public, suggesting some abnormal processing (Healey et al. 2010). However, the association between deficits in social cue perception and presentation have not been consistently associated with the expressivity dimension of negative symptoms (Hooker and Park 2002). Several studies suggest that the interplay between cognition and negative symptoms may be best considered according to each domain, for example, alogia and blunted affect may correlate more with multiple social and general cognitive deficits than does motivation (Galderisi et al. 2014; Hartmann-Riemer et al. 2015). However, poor motivation for social interaction may limit the development of social cognition (skills in expressivity) in the first place (Bellack et al. 1990) and self perception of lowered social skills may inhibit social motivation (Hooker and Park 2002; Grant and Beck 2009).

1.7.3 Premorbid Adjustment

Premorbid adjustment, as measured by Premorbid Adjustment Scale (PAS;(Cannon-Spoor, Potkin, and Wyatt 1982), encompassing 2 dimensions of social and educational functioning across four age ranges from childhood, early adolescence, late adolescence and adulthood, is associated specifically with negative symptoms in schizophrenia (Keefe et al. 1989; Buchanan et al. 1990) and FEP (Bechard-Evans et al. 2010; Chang et al. 2014; Gee et al. 2016). PAS, like negative symptoms and its correlates, is highly associated with functional outcome (Cannon-Spoor, Potkin, and Wyatt 1982). Two studies in FEP have reported that deteriorating, and to a lesser extent, stable poor PAS, is correlated with higher levels of negative symptoms compared

to stable good PAS, the latter is instead associated with higher positive symptoms (Bechard-Evans et al. 2010; Chang et al. 2014; Gee et al. 2016). Given that stable poor PAS, despite indicating more severe cognitive deficits than deteriorating PAS, is associated with lower levels of negative symptoms, adds weight to evidence of cognition and negative symptoms as unique constructs (Bechard-Evans et al. 2010). In a FEP study that controlled for the first onset of negative symptoms within the prodrome, PAS social functioning was correlated with negative symptoms while educational functioning related uniquely to cognition (Chang et al. 2014), again supporting two distinct variables that may differentially impact functioning over time.

1.7.4 Duration of untreated psychosis

The duration of untreated psychosis (DUP) is calculated as the time of the first onset of positive symptoms to the time of the initiation of appropriate antipsychotic medication (Wyatt 1991; Norman, Townsend, and Malla 2001). Reports on the length of DUP may vary according to how it is assessed. Information collected from clinical interviews may overestimate DUP while formal assessments such as The Interview for the Retrospective Assessment of the Onset of Schizophrenia (IAROS) (Häfner et al. 1992) and the Circumstances of Onset or Relapse Schedule (CORS) (Norman et al. 2004; Malla et al. 2006) that formally operationalize the start of psychosis and of treatment are likely to be more accurate (Compton, Carter, et al. 2007).

The implication from studies showing worse overall outcomes, including worst negative symptoms at baseline and follow up with longer lengths of DUP is that early intervention strategies are needed to prevent deterioration and to improve long-term trajectories (Melle et al.

2008). There have been mixed reports on the relationship between DUP and negative symptoms that have been primarily conducted within FEP samples (Chang et al. 2013; Marshall et al. 2005; Norman and Malla 2001). An investigation into heterogeneity in association between DUP and negative symptoms in FEP using latent class regression analysis suggests that discrepant findings may be explained through 3 distinct sub-groups of patients that respond differently to length of DUP (Schmitz et al. 2007). Schmitz et al (2007) reported that in one sub-group, long DUP predicted worse negative symptom outcomes, while in another group, there was an opposite effect whereby long DUP was associated with better negative symptom outcomes than was short DUP (Schmitz et al. 2007). In a third sub-group, no association between DUP and negative symptoms was found (Schmitz et al. 2007). On the other hand, a systematic review and meta-analysis of the relationship between DUP and negative symptoms that contained longitudinal data from 28 studies suggests DUP may be best considered as a dichotomous variable. Boonstra and colleagues reported that a DUP shorter than 9 months was associated with lowered negative symptoms at baseline and greater negative symptom improvement at 1-2 and 5-8 year follow up with the opposite effect for a DUP longer than 9 months (Boonstra et al. 2012). A study conducted within a FEP population suggests that an effect of DUP on negative symptoms is likely mediated through cognition and verbal memory (Chang et al. 2013), again highlighting overlap in confounders.

1.8 Negative symptoms as a predictor of outcome

1.8.1 Functioning

The importance of treating negative symptoms is highlighted first and foremost by its close relationship to functional outcomes (Herbener and Harrow 2004; Milev et al. 2005; Rocca et al. 2009). Functioning is defined broadly as a range of skills from self-preservation to basic living to relating to others in society (Tyrer and Casey 1993). While early studies suggested very poor functional outcomes for those with psychotic disorders (DSM-III) (Association 1980), more recent longitudinal data, including that from FEP (Malla and Payne 2005; Verma et al. 2012) report that a large proportion (between 8 and <75%) show fair to good social, occupational, and symptomatic recovery (Strauss and Breier 1987) (Schennach-Wolff et al. 2009; Strauss and Breier 1987) with possible cross cultural variation (Iyer et al. 2010). Higher levels of functioning are correlated with greater levels of wellbeing (Lal et al. 2014), less comorbidity (Mitchell, Betts, and Epling 2002; Dooley 2003) and better outcomes in psychosis (Mrwaha & Johnson, 2004), including less caregiver burden (Tyrer and Casey 1993). According to the Schizophrenia Working Group Consensus criteria for remission, functioning should play a vital role in any definition of remission (Andreasen et al. 2005).

In an attempt to parse out the role of negative symptoms, compared to other confounders, to functioning outcome in psychosis, several studies have been conducted. In a prospective study of 99 FEP patients, cognition as well as the severity of negative symptoms at intake, significantly predicted global functioning at 7-year follow-up with some overlap in variance between

predictors (Milev et al. 2005). A deeper investigation of distinct domains of functioning revealed a variable association of cognition and negative symptoms (Milev et al. 2005). While verbal memory alone predicted recreational activities, negative symptoms and memory combined predicted social relationships and negative symptoms with attention accounted for a significant proportion of the variance in work performance (Milev et al. 2005). In another study conducted in Canada with 141 FEP patients, a definition of remission that included negative symptoms was better at predicting outcome than was a definition of remission that included positive symptoms alone (Cassidy et al. 2009). A subsequent study with a larger sample of FEP patients from another early intervention service in Canada evaluated negative symptoms as a predictor of functioning while examining the contribution of other predictors including age of onset, DUP, PAS, medication adherence, gender, substance use, positive symptoms and verbal memory (Jordan et al. 2014). Findings from this study suggested that at the end of one (r2 adjusted = 0.35, $p < 0.001$) and two years (R2 adjusted = 0.38, $p < 0.001$), length of remission that included both positive and negative symptoms was most predictive of functional outcome, with negative symptoms playing a larger role within the 1st year, and verbal memory adding only slightly to the the model (Jordan et al. 2014). Finally, as part of a large drug trial with 1427 schizophrenia patients, negative symptoms along with a myriad of confounding and predictor variables were assessed for their impact on a range of functioning indices (Fervaha et al. 2014). Negative symptoms were significantly and inversely predictive of all domains of social, vocational and recreational functioning with a significant dose response relationship, even in patients not on antipsychotic medication (Fervaha et al. 2014). When controlling for other significant predictors including positive symptoms, extrapyramidal symptoms, depression, and anxiety, negative symptoms continued to explain a large and significant portion of the variance in functioning

(Fervaha et al. 2014). For social and recreational functioning, negative symptoms alone were the greatest predictor of outcome (Fervaha et al. 2014). Findings that negative symptoms are specifically related to social functioning has been confirmed elsewhere, though in a much smaller sample (Bowie et al. 2006). Taken together, data suggest a significant role of negative symptoms on functional outcome, that is independent of cognition and other possible confounders, across patient samples.

1.8.1.1 A note of caution: measurement overlap

Evidence from studies reporting on the relationship between functional outcome and negative symptoms, including findings by Milev et al., (2005) cited above, have been critiqued for using confounding assessment measures. For example, the Strauss and Carpenter Outcome Scale (Strauss and Carpenter 1972) and the Global Assessment of Functioning (GAF) (Jones et al. 1995) that are standard instruments to measure functioning include items for employment, school attendance, housework and close social connection that overlap with negative symptom constructs (Rabinowitz et al. 2012). More recent studies have attempted to overcome this by removing items from either negative symptom (ex. (Mohamed et al. 2008) or functioning assessments (ex. (Rabinowitz et al. 2012) that share too much variance. Overall, it has been reported that correlations between scales are still divergent enough to indicate measurement of separate entities (Rabinowitz et al. 2012; Jordan et al. 2014).

1.8.2 Quality of life

Quality of life (QofL) is increasingly considered a measure of illness-outcome that is thought to reflect one's subjective experience of wellbeing (Lal et al. 2014). The scale that is most often used in psychosis populations is the Quality of Life Scale (QLS), a semi-structured interview with 21-items measuring material and physical wellbeing, relationships with people, social and community activities, personal fulfillment and recreation (Heinrichs, Hanlon, and Carpenter Jr 1984; Fervaha et al. 2014). It can, however, be argued that QLS measures aspects of functioning and, even, negative symptoms and not subjective QOL. Negative-symptom-severity most predicts levels of wellbeing in schizophrenia as compared to positive, including disorganized, symptoms (Browne et al. 2000; Ho et al. 1998; Priebe, Roeder-Wanner, and Kaiser 2000). Findings from a study in FEP that used a general wellbeing survey (Dupuy 1984) and the QLS scale to determine their correlation to negative symptoms found that while the QLS scale correlated highly with negative symptoms, the general wellbeing survey showed an opposite pattern and correlated instead with positive symptoms (Norman et al. 2000). A more recent meta-analysis that examined both cross-sectional and longitudinal correlations between quality of life and symptoms suggests that in the first phase of illness, positive symptoms may have a stronger role but that negative symptoms are more likely to affect quality of life in the later stages of illness (Eack and Newhill 2007).

1.8.3 Medication adherence

Medication adherence is considered integral to recovery in psychotic disorders (world health organization, 2011) and in particular during the few years following a FEP, when long – term recovery may be established. Rates of medication adherence are often less than 50% (Rabinovitch et al. 2009; Leclerc et al. 2015). While negative symptoms have been implicated in lower medication adherence through impaired skills for self care (Roca et al. 2007) or lack of motivation (Velligan, Weiden, et al. 2009), a cross sectional study has reported an opposite effect (Rettenbacher et al. 2004) supporting greater adherence with higher levels of negative symptoms. Overall the data is inconclusive (Acosta et al. 2012; Fleischhacker, Oehl, and Hummer 2003) and further studies are needed (Velligan, Weiden, et al. 2009).

1.9 Rationale and thesis objectives

A shift in focus onto negative symptoms in psychotic disorders has revealed that this domain is critical to the conceptualization of the disorder. Negative symptoms have a complex structure and interface with other factors that make them a challenge to discern. As negative symptoms most strongly predict functioning, arguably the most important outcome following any illness, determining the optimal course of treatment is paramount. With no effective biological interventions available, recommendations have encouraged the use of psychological and psychosocial interventions as an add-on treatment to medication. However, there is a dearth of research to support the benefit of this practice. This thesis therefore, aims first to provide evidence for the effectiveness of the range of available psychological and psychosocial interventions for negative symptoms in psychotic disorders. The second objective of my investigation was to survey the trajectory of negative symptoms over an initial 2 years of

specialized early intervention (EI) and to determine whether improvements made within the first 2 years are maintained or even further improved over the subsequent 3-years, with any differential advantage of extending EI. The final goal of my work was to examine the structure, including any nuanced course of negative symptom domains, that may increase our understanding of treatment application and outcome. My work is embedded within a specialized early intervention (SEI) framework that aims to support FEP patients at a phase of illness where improved long-term trajectories may be best realized.

The following papers are presented: A) A sample of 206 Canadian psychiatrists who treat patients with psychotic symptoms were surveyed for their knowledge and practice with persistent negative symptoms. We found that while the majority of psychiatrists observed high levels of negative symptoms and recognized them as an obstruction to functioning and quality of life, they did not know of any effective available treatment. B) A meta-analysis and systematic review of English-language, randomized, controlled-trialed studies investigating psychosocial and psychological interventions for psychosis with reports of negative-symptom outcomes. Findings from this review suggest a significant effect of cognitive behavioural therapy (CBT), skills-based training, music and exercise interventions on negative symptom outcomes. We found a significant effect of specialized early intervention, as a package of evidence based treatments, in the earliest phase of illness (FEP), along side the need for establishing the long-term, post-treatment, benefits of such treatment on negative symptoms C) A protocol for an RCT to determine whether specialized early-intervention for the full 5 year critical period compared to the standard 2 years of specialized early-intervention followed by 3-years of regular care in the community would better support sustained and even further benefits of treatment, and

particularly, increased length of remission D) An investigation of secondary outcomes, namely, of total negative symptoms, embedded within the larger RCT. This study revealed that over the first 2 years of EI, the level of negative symptoms decreased significantly. We found additional improvements in total negative symptoms post randomization, with no differential impact of extended EI. An analysis of negative symptom constructs of motivation and expressivity over time suggests each have a unique course with motivational deficits showing an early (within the first 2 years) but more restricted window of amelioration compared to expressivity that takes longer to begin improving but that then continues to decrease for up to 3.5 years from the first onset of EI treatment.

Thesis organization:

Chapter 1: Introduction to psychotic disorders and to negative symptoms

Chapter 2: 'Persistent negative symptoms in schizophrenia: survey of Canadian psychiatrists'

Chapter 3: 'Psychological and psychosocial interventions for negative symptoms in psychosis: systematic review and meta-analysis.'

Chapter 4: Extends a discussion on our findings of the benefit of Specialized Early Intervention in First Episode Psychosis with an overview of models of EI, a current understanding of FEP and of a 'critical period' of intervention.

Chapter 5: 'A five-year randomized parallel and blinded clinical trial of an extended specialized early intervention vs. regular care in the early phase of psychotic disorders: study protocol'

Chapter 6: 'Progress of Negative Symptoms during the Critical Period of the Initial Five Years of a First Episode of Psychosis'

Chapter 7: Discussion and conclusions

Chapter 2: 'Persistent negative symptoms in schizophrenia: survey of Canadian psychiatrists'

research paper

Persistent negative symptoms in schizophrenia: survey of canadian psychiatrists

Danyael Lutgens,[1] Martin Lepage,[2] Rahul Manchanda[3] and Ashok Malla[4]

[1]PhD Candidate, mcgill university Department of Psychiatry; Prevention and early Intervention Program for the Psychoses, Douglas mental Health university Institute, montreal, Quebec, Canada

[2]Associate Professor, Department of Psychiatry, mcgill university, montreal, Quebec; Prevention and early Intervention Program for the Psychoses, Douglas mental Health university Institute, montreal, Quebec, Canada

[3]Professor, Department of Psychiatry, Western university, ontario; medical Director, Prevention and early Intervention Program for the Psychoses, london Health sciences Centre, london, ontario, Canada

[4]Professor, Department of Psychiatry, mcgill university, montreal, Quebec; Director, Prevention and early Intervention Program for the Psychoses, Douglas mental Health university Institute, montreal, Quebec, Canada, email ashok.malla@douglas.mcgill.ca

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A sample of 206 Canadian psychiatrists who routinely treat patients with psychotic disorders were randomly surveyed regarding their knowledge and practice in relation to persistent negative symptoms of schizophrenia. Large majorities reported observing a high prevalence of persistent negative symptoms that do not respond to available treatments (83%), have a profound impact on functional outcomes (96.5%) and contribute to family burden. almost half the sample (43%) recognised the importance of formally assessing persistent symptoms and nearly a third (30%) indicated that this was a part of their usual practice. these survey results correspond with recent consensus and highlight the importance and challenge of treating persistent negative symptoms in schizophrenia.

Negative symptoms, a distinct domain of schizophrenia, represent a fundamental challenge to treatment protocols (Kirkpatrick *et al*, 2006). This cluster of symptoms, comprising affective flattening, poverty of thought, anhedonia/asociality, avolition and poor motivation (Andreasen & Olsen, 1982), is conceptualised as either primary deficits (core deficits of schizophrenia) or secondary deficits – resulting either as medication side-effects or from other symptoms such as depression (Möller, 2003). These symptoms are present in a majority of patients during their first episode of psychosis (Malla *et al*, 2002). A smaller proportion (20–30%) have sustained primary negative symptoms that are defined as persistent negative symptoms (Buchanan, 2007). The importance of treating negative symptoms is highlighted by their strong association with quality of life (Bow- Thomas *et al*, 1999), social functioning (Corcoran *et al*, 2011), interpersonal relationships, work performance and overall functional outcomes (Milev *et al*, 2005); they are also of great importance to carers and contribute to community burden (Perlick *et al*, 2006).

Despite the serious implications of negative symptoms, few effective pharmacological treatments are available for primary negative symptoms, which, therefore, tend to persist (Malla *et al*, 2002). According to expert consensus, clinical recogni tion and understanding of negative symptoms is the first step in improving functional outcomes (Malla *et al*, 2002). However, the often insidious and relatively complex nature of negative symptoms (Kirkpatrick *et al*, 2006), lack of adequate pharmacological treatment (Malla *et al*, 2002), possible benefit from psychosocial interventions (Barnes & Paton, 2011) and the potential for new treatment discoveries highlight the importance of current physician perspectives, knowledge and practices. The aim of this pilot study was to explore broadly how Canadian psychiatrists who regularly treat patients with psychotic disorders conceptualise, evaluate and treat persistent negative symptoms in schizophrenia in the light of recent developments i n this field. No *a priori* hypothesis was considered.

Method

Psychiatrists listed in the Canadian Medical Directory, including those from the Canadian Psychiatric Association and Association des Médecins de Psychiatres du Québec (which have a combined total of 3500 registered members), were contacted to ask for their participation in a survey on negative symptoms if they routinely treated patients with a psychosis. They were given the option of participation via a secure website or by post (with a paper copy). Two hundred and six agreed to participate: 127 (62%) by post and 79 online (38%).

Ethical approval for the study was obtained from the Douglas Mental Health University Institute.

The questionnaire for the study was designed by the investigators to obtain psychiatrists' perspectives on persistent symptoms in schizophrenia as seen in their clinical practice. There were 13 questions regarding knowledge of negative symptoms and several items relating to persistent positive symptoms (the latter are not included here, given the scope of this report). The questions concerned: negative symptoms and potential confounds such as extrapyramidal symptoms and depression; level of awareness; the efficacy of treatment options; the relevance of such symptoms for functional outcomes; and their effect on carers. Each item was scored on a five-point Likert scale. Details of the survey instrument are available upon request from the authors.

Simple frequencies were computed for phys- ician demographics and responses using Statistical Package for the Social Sciences (SPSS, version 18).

Results

Respondents came from a range of settings and indicated an average of 21 years in practice (s.d. 12.64, $n = 179$). More than half of all respondents were male (60%, $n = 124$). Their mean age was 53 (s.d. 12.75, $n = 188$).

Frequency and visibility of symptoms

Comparatively large proportions of psychiatrists reported observing asociality (n = 92, 46%), avolition (n = 91, 45%) and flat affect (n = 71, 36%) 'very frequently' (i.e. in 50–74% of patients) in patients with psychotic disorders in their clinical practice. Anhedonia and alogia were rated as being seen 'frequently' (25–49% of patients) by 89 (44%) and 72 (36%), respectively. Specifically in first-episode psychosis (FEP), the prevalence of negative symptoms was rated at 25–49% of patients by 93 psychiatrists (46%). Respondents largely 'agreed' or 'strongly agreed' that they could distinguish between negative symptoms and overlapping symptoms (e.g. extrapyramidal symptoms and depression) (n = 150, 76%) (for complete responses, see Table 1).

The impact of persistent symptoms

A large majority of psychiatrists (n = 142, 71%) rated the contribution of negative symptoms to functioning as 'very important' and an additional 51 (26%) reported this relationship to be 'impor- tant'. Similarly, a large majority of psychiatrists (n = 179; 90%) indicated that negative symptoms were 'frequently' or 'always' a burden to carers. Avolition/apathy was rated as the largest burden by 148 (89%) psychiatrists.

A large number of psychiatrists endorsed the statement 'positive symptoms can lead to persistent negative symptoms' ('agree'; n = 81, 40%), while a smaller number (n = 71, 35%) were undecided about this. For complete responses, see Table 1.

Treatment of negative symptoms

Only 13.5% of respondents (n =27) rated second-generation antipsychotics as 'effective' (in 50–74% of patients) or very effective (n = 5, 3%). Psychiatrists rated antidepressants as being 'ineffective' (n=95, 48%; effective in only 11–24% of patients), or 'somewhat effective' (n = 86, 43%; 25–49% of patients) in treating negative symptoms. A large number of psychiatrists (n =119, 60%) rated cognitive–behavioural therapy (CBT) as 'somewhat effective' (of benefit for 25–49% of patients) in the treatment of negative symptoms but only a minority (n=33, 17%) rated it as being 'effective' or 'very effective'. For complete responses, see Table 2.

Discussion

Given the implications of persistent negative symptoms and the difficulty in treating them, knowledge of the issue is imperative for clinicians in the field. Our survey findings corroborate recent consensus guidelines (Kirkpatrick *et al*, 2006) and suggest that the responding Canadian psychiatrists in this study see negative symptoms in psychosis as widely prevalent, resistant to treatment and of great consequence for functional outcomes in patients with psychotic disorders. This is generally in agreement with findings from both epidemiological (Malla *et al*, 2002) and clinical studies (Malla *et al*, 2011).

Our survey data indicate that the majority of psychiatrists consider persistent negative symptoms in psychosis to have an impact on functional outcomes and to increase carer burden, especially in relation to the domain of avolition/apathy. The high endorsement of the relationship between negative symptoms and functional outcome is supported by research findings (Milev *et al*, 2005).

Interestingly, half of the responding psychiatrists (50%) 'agreed' or 'strongly agreed' that persistent positive symptoms were a problem because of their effect on negative symptoms. This view is consistent with recent characterisations of the longitudinal relationships between symptoms, and emphasises the importance of monitoring secondary negative symptoms when positive symptoms worsen (Möller, 2007). Further, this may also reflect a belief psychiatrists hold that persistent positive symptoms lead to increases in negative symptoms over time, possibly due to some unknown toxicity. Such a hypothesis has been suggested in relation to the effects of prolonged duration of untreated psychosis (Malla *et al*, 2011).

Only a minority of this sample of psychiatrists regarded antipsychotics (16%) or CBT (18%) as an effective treatment for negative symptoms. This view of antipsychotics is likely based on clinical experience. Antidepressants were rated by virtually all psychiatrists as being at best somewhat effective in the treatment of negative symptoms. While antidepressants may work in treating negative symptoms secondary to depression, they have been shown to be largely ineffective with persistent negative symptoms (Barnes & Paton, 2011). This perspective is consistent with research evidence (Malla *et al*, 2002). It would, therefore, appear that this sample of psychiatrists no longer accept that second-generation antipsychotics are likely to be effective in treating negative symptoms. Possibly this is also related to the psychiatrists' reported clinical ability to distinguish secondary from primary negative symptoms. The overall ability of clinicians to discriminate among symptoms lends clinical validity to evidence that negative symptoms in psychosis are a unique and independent construct that may now be better measured (Foussias *et al*, 2009; Cassidy *et al*, 2012), and that can be specifically targeted for treatment if effective treatments were to become available (Malla *et al*, 2002).

The level of experience psychiatrists have with the use of CBT is unknown but is anyway likely to be less than with the use of antipsychotic medication. CBT is reported to be somewhat more promising than antipsychotic or antidepressant medications (Rector & Beck, 2001; Wykes *et al*, 2008). The utility of CBT, however, may be undermined in particular contexts. Moreover, CBT for negative symptoms is not widely available and is traditionally provided over relatively long periods of time. Further, CBT may not be appropriate for all patients, depending on their level of functioning (Lehman *et al*, 2004).

Our results likely represent the opinion of only those psychiatrists who frequently treat patients with psychotic disorders and who volunteered to participate. The selection may well have been

Table 1
Frequency, visibility and impact of symptoms: *n* (%)

How often do you see the following negative symptoms in your patients?	Almost always (>75% of patients)	Very frequently (50–74%)	Frequently (25–49%)	Occasionally (11–24%)	Rarely (<10%)
Asociality	30 (15%)	92 (46%)	61 (30%)	12 (6%)	6 (3%)
Avolition	44 (22%)	91 (45%)	46 (23%)	14 (7%)	6 (3%)
Anhedonia	13 (7%)	64 (32%)	89 (44%)	29 (14%)	6 (3%)
Alogia	15 (8%)	39 (20%)	72 (36%)	49 (25%)	24 (12%)
Flat affect	30 (15%)	71 (36%)	60 (30%)	30 (15%)	7 (4%)
According to you, what is the prevalence of negative symptoms at the onset of psychosis (first episode)?	0–10%	11–24%	25–49%	50–74%	> 75%
	3 (2%)	26 (13%)	93 (46%)	61 (30%)	18 (9%)
As part of my clinical practice, it is possible for me to distinguish between negative symptoms and depression or Parkinsonism	Strongly agree	Agree	Undecided	Disagree	Strongly disagree
	33 (17%)	117 (60%)	37 (19%)	11 (6%)	–
How important is the contribution of negative symptoms to functional outcome in persons with schizophrenia?	Unimportant	Of limited importance	Moderately important	important	Very important
	–	–	7 (4%)	51 (26%)	142 (71%)
in your practice, do you observe that negative symptoms cause increased burden for caregivers of patients with such negative symptoms?	Always	Frequently	Occasionally	Rarely	Never
	43 (22%)	136 (68%)	18 (9%)	2 (1%)	1 (1%)
Persistent positive symptoms can lead to persistent negative symptoms	Strongly agree	Agree	Undecided	Disagree	Strongly disagree
	18 (9%)	81 (40%)	71 (35%)	32 (16%)	–

Not all respondents answered all questions. Percentages relate to number of responses on each item.

Table 2
Treatment and assessment of symptoms

Assessment	Always	Frequently	Occasionally	Rarely	Never
Do you routinely assess negative symptoms?	90 (45%)	87 (43%)	24 (12%)	1 (1%)	–
if so, do you use any rating scales or any specific questions?	22 (11%)	49 (24%)	57 (28%)	41 (20%)	33 (16%)
Treatment	Very effective (of benefit for >75% of patients)	Effective (50–74%)	Somewhat effective (25–49%)	Ineffective (11–24%)	Very ineffective (<10%)
How effective are atypical antipsychotics for the treatment of negative symptoms of schizophrenia?	5 (3%)	27 (13%)	101 (50%)	60 (30%)	9 (5%)
How effective are antidepressants for the treatment of negative symptoms of schizophrenia?	1 (1%)	5 (3%)	86 (43%)	95 (48%)	14 (7%)
How effective is cognitive–behavioural therapy for the treatment of negative symptoms of schizophrenia?	1 (1%)	32 (16%)	119 (60%)	44 (20%)	4 (2%)

Not all respondents answered all questions. Percentages relate to number of responses on each item.

biased towards those psychiatrists in this field who are more knowledgeable about negative symptoms. This would suggest the need for a greater effort to increase knowledge and awareness of the importance of persistent negative symptoms among the profession in general.

Despite the limitations of a relatively small sample size, this study represents, to our knowledge, the first survey to examine the state of knowledge and practice patterns of Canadian psychiatrists who work with patients suffering from psychotic disorders.

Our findings suggest the clinical validity and translation of current knowledge of persistent symptoms in clinical practice. However, while psychiatrists emphasised the importance of formally assessing persistent symptoms, few actually carried this out in practice, suggesting that some symptoms may be undetected. Future research may investigate means to increase the use of structured negative symptom assessment in clinical practice.

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Review article

Psychological and psychosocial interventions for negative symptoms in psychosis: systematic review and meta-analysis

Danyael Lutgens, Genevieve Gariepy and Ashok Malla

Background
Negative symptoms observed in patients with psychotic disorders undermine quality of life and functioning. Antipsychotic medications have a limited impact. Psychological and psychosocial interventions, with medication, are recommended. However, evidence for the effectiveness of specific non-biological interventions warrants detailed examination.

Aims
To conduct a meta-analytic and systematic review of the literature on the effectiveness of non-biological treatments for negative symptoms in psychotic disorders.

Method
We searched for randomised controlled studies of psychological and psychosocial interventions in psychotic disorders that reported outcome on negative symptoms. Standardised mean differences (SMDs) in values of negative symptoms at the end of treatment were calculated across study domains as the main outcome measure.

Results
A total of 95 studies met our criteria and 72 had complete quantitative data. Compared with treatment as usual cognitive–behavioural therapy (pooled SMD −0.34, 95% CI −0.55 to −0.12), skills-based training (pooled SMD −0.44, 95% CI −0.77 to −0.10), exercise (pooled SMD −0.36, 95% CI −0.71 to −0.01), and music treatments (pooled SMD −0.58, 95% CI −0.82 to −0.33) provide significant benefit. Integrated treatment models are effective for early psychosis (SMD −0.38, 95% CI −0.53 to −0.22) as long as the patients remain in treatment. Overall quality of evidence was moderate with a high level of heterogeneity.

Conclusions
Specific psychological and psychosocial interventions have utility in ameliorating negative symptoms in psychosis and should be included in the treatment of negative symptoms. However, more effective treatments for negative symptoms need to be developed.

Declaration of interest
None

Negative symptoms, characterised by an absence or reduction of affective, as well as social and behavioural expression, are regarded as an inherent aspect of psychotic disorders and among the most important predictors of quality of life[1] and functional outcome.[1–3] Further, negative symptoms may be transitory and secondary to depression and side-effects from antipsychotic medication,[4] whereas persistent negative symptoms are often regarded as primary to the underlying disease process.[4] Persistent negative symptoms are present in 25% of patients with first-episode psychosis (FEP)[5] and in an even greater proportion of patients with chronic schizophrenia.[6,7] Antipsychotic medications, highly effective for the treatment of positive symptoms, and newer biological treatments such as transcranial magnetic stimulation, have at best a modest impact on negative symptoms.[8] Given the paucity of options available to treat negative symptoms, current best practice suggests the use of psychological and psychosocial interventions in addition to medication.[9,10] The evidence supporting the effectiveness of such interventions for negative symptoms has, however, not been fully explored. Reviews on psychological and psychosocial treatment options have focused largely on positive symptoms and relapse prevention[11–14] with two exceptions[15,16] that presented negative symptom outcomes as their primary objective. In their meta-analysis, Fusar-Poli and colleagues[15] pooled negative symptom outcomes from a broad range of primarily biological and some psychological interventions. They aggregated all negative symptom outcome data from a limited number of psychological interventions into a single effect size, limiting the interpretation for different psychological and psychosocial treatments. In a narrative analysis of results of randomised control trials (RCTs) of psychological interventions with negative symptom outcomes,[16] alternative intervention types such as arts- and exercise-based therapies were excluded and a stringent systematic review of the literature including quality ratings was not performed. Our study extends previous work by providing a systematic review and complete qualitative and quantitative synthesis of the current literature on the effectiveness of all psychological and psychosocial interventions for the treatment of negative symptoms in psychotic disorders.

Method

Search strategy
We searched the following five major databases: MEDLINE via PubMed, Embase, Web of Science, PsycINFO and the Cochrane Library. Articles from inception to 19 October 2015 were included in our search. Database-specific search terms included the key words 'psychosis', 'schizophrenia', 'negative symptoms', 'therapy' and 'intervention' with diagnosis-specific and symptom-specific subtypes and relevant variations and synonyms (online supplement DS1). We searched only English-language publications and identified additional studies through hand searches of bibliography from primary studies, review articles and key journals, as well as through contacts with experts in the field (Fig. 1).

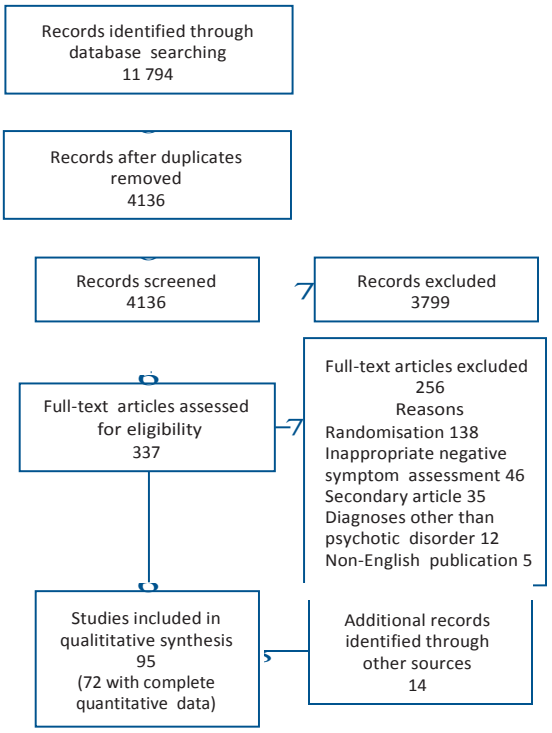

Fig. 1 PRISMA flow diagram.

Inclusion/exclusion criteria

Studies were included if they met the following criteria: RCT design; investigation of a psychological or psychosocial intervention; report of negative symptom outcomes using a valid and reliable negative symptom measurement (such as the Scale for Assessment of Negative Symptoms (SANS), the Negative Symptom subscale of the Positive and Negative Symptom Scale (PANSS)); a majority sample with a diagnosis of a schizophrenia spectrum or other non-organic psychotic disorder. Random crossover trials were included, although only between-group comparisons data, prior to the crossover, were extracted. We excluded the following types of studies: those published in a language other than English; quasi-experimental study designs; theoretical papers; case studies; meta-analyses; other reviews; qualitative reports and designs utilising cluster random trials as well as medication efficacy trials even if the latter used a psychological or psychosocial intervention as a supplementary treatment.

Screening

The first author (D.L.) and a research assistant independently screened all citation titles for their broad applicability using computer-based software (Distiller SR[17]). Titles that clearly did not meet inclusion criteria were removed from citation listings. At the second stage a more detailed independent screening by both raters was conducted on all abstracts. Disagreements at both the first and second screening were resolved between the first author (D.L.) and research assistant through discussion with the senior author (A.M.). The first author (D.L.) extracted the full texts of selected articles for the final screening (Fig. 1).

Data extraction and quality assessment

Information on the nature of the experimental intervention and control, characteristics of the study sample, outcome measures and effect sizes were extracted. Study quality was assessed from a critical appraisal checklist.[18–21] on standardisation of treatment, recruitment, sequence generation, allocation concealment, comparability of groups, equality of care between groups, masked assessment, inclusion/exclusion criteria, attrition, adherence and intention-to-treat analysis. Studies were considered to be of poor quality if they presented high or unclear risk of bias for either the sequence generation or allocation concealment, or presented two or more risks of bias. Sample size was not included within the measure of quality. Disagreements on quality were resolved by discussion among authors (D.L., G.G. and A.M.).

Quantitative analysis

A quantitative summary of the literature was obtained through meta-analytic methods. Measures of effect were calculated from data available or from standard errors reported (n = 72 studies). Standard mean difference (SMD) reported, or Cohen's d can be interpreted such that 0.2, 0.5, and 0.8 are equated with effect sizes of small, medium, and large.[22] Studies for which such data were not available were included in the qualitative analysis only. We pooled estimates using the DerSimonian & Laird random-effects model. High heterogeneity between studies was expected and evaluated through I^2 tests as well as through stratified analysis by type of intervention, control and study quality. Publication bias was determined with a funnel plot that provides a visual representation of how the odds ratio for each individual study varied from the pooled odds ratio. Analyses were conducted in Stata 12.1. No data of negative symptom outcomes for controls within treatment as usual (TAU) and waitlist conditions post treatment end are included in this review. Several RCTs included either two active controls or an active control alongside a TAU group. In such cases, for the overall pooled effect size, we included only the TAU group as this was the comparison control used most often across studies. Post-treatment follow-up data are described qualitatively. The PRISMA checklist was followed for the reporting of all outcomes.[23] The protocol for this review is available on PROSPERO (CRD42014015244).

Results

Study selection

A total of 11 794 publications were initially retrieved and, after removing duplicates and adding studies from hand searches, 4150 publication citations remained for broad screening. A further 3799 studies were excluded. Pharmacological trials and studies without a randomisation design were the main reasons for exclusion. A total of 95 studies that met the inclusion criteria were thus identified (Fig. 1).[23] Of these, 72 studies provided data on negative symptom outcome and were included in the meta-analysis.

Cognitive–behavioural therapies (CBT)

A total of 26 studies investigated the effectiveness of CBT in psychosis.[24–53] Of these, two were CBT interventions adapted specifically for treating negative symptoms.[28,29,39] Highly significant heterogeneity between CBT studies was found, I^2 = 73.6%, P<0.001 (online Table DS1). Details of study characteristics are presented in Table DS2. Treatment was offered over a mean of 6 months (range 1.25–18) for a mean of 28 sessions, each session lasting a mean of 66 min (range 45–90).

Overall, evidence indicated CBT to be an effective intervention for negative symptoms (pooled SMD −0.34, 95% CI −0.55 to −0.12, Fig. 2(a)). Compared with TAU, 59% (10/17) of studies reported CBT to be more effective at the end of treatment (pooled

SMD −0.43, 95% CI −0.55 to −0.30). Compared with active control, none of 12 studies suggest a benefit of CBT (pooled SDM −0.11, 95% CI −0.26 to 0.04), although 7 reported substantial but equal improvements in both active conditions. For studies that reported long-term follow-up (mean 27 months), CBT was beneficial compared with TAU across 57% (8/14) of the comparisons. None of the studies with active controls reported such effect, except for one using befriending as the active control.[31,54] There were no differences in effects as a result of differences in study quality.

Skills training, occupational therapy and cognitive adaptation training

A total of 17 RCTs using skills training ($n = 11$),[55–65] occupational therapy ($n = 3$),[66–68] cognitive adaptation training ($n = 2$)[69,70] or vocational training ($n = 1$)[71] were included. Only one study was designed specifically to treat negative symptoms[65] and there was highly significant heterogeneity between studies, $I^2 = 85.8\%$, $P < 0.001$ (online Table DS1). Study characteristics are available in Table DS3. Treatment was offered over a mean of 7 months (range 1.5–24) for a mean of 25.5 sessions (range 12–76) with a mean length of 86 min per session (range 45–180). One active control study compared two variations of skills training: social skills and relapse prevention skills.[58]

Overall 53% (9/17) of the studies favoured the experimental intervention at the end of treatment (pooled SMD −0.44, 95% CI −0.77 to −0.10, Fig. 2(a)). This effect was largely driven by studies using TAU as the control (pooled SMD −0.42, 95% CI −0.56 to −0.28) and was not present in studies using an active control (pooled SMD −0.05, 95% CI −0.30 to 0.19). Stratified analyses indicated a significant effect of skills training (pooled SMD −0.31, 95% CI −0.45 to −0.17) and of occupational therapy (pooled SMD −1.00, 95% CI −1.48 to −0.51) only. In the study that compared different skills-training programmes, no significant differences were reported.[58] High- and medium- quality studies reported more favourable outcomes (pooled SMD −0.42, 95% CI −0.56 to −0.28) than those of low quality (pooled SMD 0.00, 95% CI −0.26 to 0.26). Of five studies with follow-up negative symptom data,[57,61–63,69] three favoured the experimental intervention at 1 month,[63] 3 months[61] and 6 months.[62] The benefit of skills training over social milieu therapy that was reported at 3 months was not maintained at 6-month follow-up in one study.[61]

Neurocognitive therapies

A total of 16 studies used neurocognitive interventions including cognitive remediation ($n = 11$);[72–82] cognitive training ($n = 2$);[83,84] cognitive rehabilitation ($n = 1$);[82] neurocognitive therapy ($n = 1$);[85] and cognitive enhancement ($n = 1$).[86] Another study focused on improving cognitive strategies related to attention, verbal memory and planning.[87] Three interventions studied were designed primarily to improve negative symptom outcomes[76,83,87] (see online Table DS4 for study characteristics). There was highly significant heterogeneity between studies, $I^2 = 74.2\%$, $P < 0.001$ (online Table DS1). Across studies, treatment was offered over a mean of 3.75 months (range 2–24) with a mean of 42 sessions (range 16–120), delivered for a mean of 76 min (range 15–150). Seven studies utilised computer technology for treatment delivery[77,78,80–82,86,87] including two specifically designed for the amelioration of negative symptoms.[83,87] Active controls included computer games[81] and supportive therapy.[86]

Neurocognitive interventions were effective in only a minority of studies ($n = 5$, 31%) and data show no overall effect (pooled SMD −0.15, 95% CI −0.41 to 0.11, Fig. 2(b)), regardless of control type and/or study quality. No significant differences were found between modes of neurocognitive treatment delivery.[78,87] Two of five studies with long-term follow-up data[72–74,77,87] reported a significant effect at 3 months[84] and 9 months,[85] and another study reported a significant benefit of cognitive remediation at 4- but not at 9-month follow-up, compared with group leisure activities.[72]

Exercise therapy

Ten RCTs of exercise therapy on negative symptoms[88–97] were reported (see online Table DS5 for study characteristics). Exercises investigated were yoga,[89,90,92,94] aerobic,[91,93] resistance training,[97] structured walking, tai chi[88] and traditional dance.[96] Of these only one study was designed to measure negative symptoms as a primary outcome.[88] Significant heterogeneity between studies was found, $I^2 = 54.8\%$, $P = 0.039$ (online Table DS1). Exercises were offered over a mean of 3 months (range 2 weeks to 8 months) with an average of 26.7 sessions (range 8–48) and a mean of 53 min per session (range 40–60).

An effect of exercise on negative symptoms was found (pooled SMD −0.36, 95% CI −0.71 to −0.01, Fig. 2(b)) that was largely the result of four of seven (57%) comparisons with TAU (pooled SMD −0.42, 95% CI −0.76 to −0.09) whereas active control comparisons showed no effect (pooled SMD −0.07, 95% CI −0.37 to 0.23). Overall, lower-quality studies showed greater effects (pooled SMD −0.37, 95% CI −0.74 to −0.00) than higher-quality studies (pooled SMD 0.14, 95% CI −0.42 to 0.14). Resistance training and exercise as active control comparisons were equally effective in treating negative symptoms.[97] Too few studies were available to warrant a comparison of differences in exercise intervention types. None of the three studies with follow-up assessments found any treatment effect at 1 month,[92] 1.5 months[88] and 3 months.[94]

Art and music therapies

Seven RCTs were art- or music-based interventions: two fine arts[98,99] and five music based[100–104] (see online Table DS6 for study characteristics) with highly significant heterogeneity between studies, $I^2 = 94.9\%$, $P < 0.001$ (online Table DS1). Treat- ment was offered over a mean of 4.25 months (range 1–12 months), for a mean of 22 sessions (range 10–52) with a mean of 62.5 min (range 45–90) per session.

Considered together, arts-based treatments were not effective at treating negative symptoms with 57% (4/7) demonstrating no effect (pooled SMD −0.14, 95% CI −0.78 to 0.50, Fig. 2(b)). However, whereas fine-arts-based therapies were not advantageous (pooled SMD 0.57, 95% CI 0.41–0.74), sensitivity analysis revealed a distinct benefit of music-based therapies compared with TAU (pooled SMD −0.58, 95% CI −0.82 to −0.33).[101,103,104] There were no differences in end-of-study outcomes as a result of differences in study quality. Three studies with follow-up data reported no significant lasting[99,104] or emerging[98,99] benefit.

Family-based interventions

Six RCTs investigating family-based interventions reported negative symptom outcomes[105–110] (see online Table DS7 for study characteristics) with marginally significant heterogeneity between studies, $I^2 = 65.4\%$, $P = 0.056$ (online Table DS1). The mean duration of treatment was 10.9 months (range 2.5–18) with a mean of 23 sessions (range 10–45) and the mean session duration of 97.5 min (range 60–120).[105,106,108,110] One study did not provide standardised treatment[106] and two did not specify.[109,110] Family interventions were delivered within: multiple

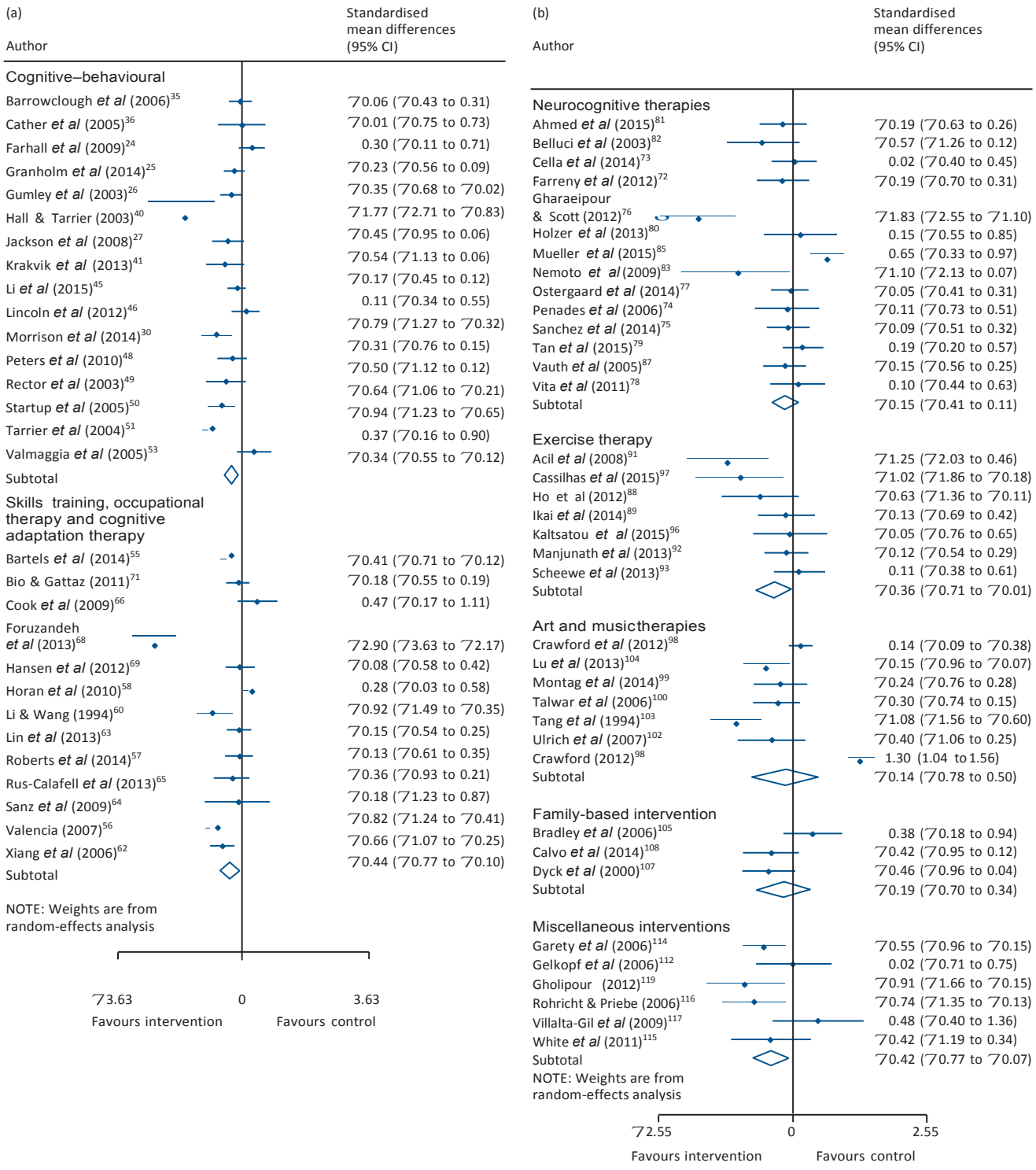

Fig. 2 Forest plots.

(a) Cognitive–behavioural therapy, skills training, occupational therapy and cognitive adaptation therapy; (b) neurocognitive therapies, exercise therapy, art and music therapies, family-based interventions and miscellaneous interventions.

family groups,[106,107,109] single family groups[110] or a combination of both.[105,108] One study also used individualised sessions of psychotherapy.[109] All studies focused primarily on providing psychoeducation;[105–109] two studies also included large components of social-skills training.[106,110] Only one study was designed to measure negative symptom outcomes.[107]

No effect of family intervention was detected either individually or overall (pooled SMD −0.19, 95% CI −0.70 to 0.34) regardless of control comparison. There were no differences in end-of-study outcomes as a result of differences in study quality. Neither of the two studies with follow-up reported a significant effect.[109,110]

Miscellaneous interventions

The following unclassified interventions (n = 10) were included: humour therapy (n = 2);[111,112] specialised early intervention for FEP (SEI: n = 2);[113,114] acceptance and commitment therapy (n = 1);[115] body psychotherapy (n = 1);[116] dog-assisted psychological

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treatment (n = 1);[117] adherence therapy (n = 1);[118] token therapy (n = 1);[119,120] and motivation approach to learning arithmetic (n = 1).[120] Body psychotherapy, motivational learning and humour therapy were designed specifically to treat negative symptoms (see online Table DS8 for study characteristics). Heterogeneity between studies was found to be non-significant, I^2 = 33.3%, P = 0.174 (online Table DS1). The mean duration of treatment was 2.25 months (range 1–3), excluding both SEI studies that were conducted over a span of 1.5 years[114] and 2 years.[113] Whereas SEI interventions were intensive over the entire period of 1.5–2 years, for the other studies mean number of sessions offered was 24 (range 8–60) over an average session length of 66 min (range 30–120).

A significant effect of all miscellaneous studies was found (pooled SMD −0.42, 95% CI −0.77 to −0.07, Fig. 2(b)) driven largely by TAU as opposed to active control comparisons (pooled SMD −0.48, 95% CI −0.75 to −0.21; pooled SMD −0.33, 95% CI −0.67 to 0.02, respectively). Higher-quality studies reported greater overall effects (pooled SMD −0.61, 95% CI −0.87 to −0.36) compared with low-quality studies (pooled SMD 0.08, 95% CI −0.37 to 0.52). Compared with supportive counselling, body psychotherapy was found to be more effective and the effect was retained at 4-month follow-up (pooled SMD −0.74, 95% CI −1.35 to −0.13).[116] Token therapy was more effective than TAU (pooled SMD −0.91, 95% CI −1.66 to −0.15) but not active control (exercise). Treatment in an SEI service was more effective than TAU (regular care) (pooled SMD −0.38, 95% CI −0.53 to −0.22) but the effect was not retained after transfer to regular care.[121] Compared with TAU, adherence therapy[118] and acceptance and commitment therapy[115] were not effective. Token therapy was not more effective on negative symptoms than an exercise active control.[119] Overall, medium- and high-quality studies were more likely to report a significant effect at end of treatment (pooled SMD −0.61, 95% CI −0.87 to −0.36) than were low-quality studies (pooled SMD 0.08, 95% CI −0.37 to 0.52).

Additional analyses

The above results raise several other questions for which we conducted the following additional analyses.

Is the impact of interventions greater in the early v. later phases of illness?

Using study reports of mean patient age as a proxy measure of early *v.* later phase we used a cut-off of 35 years, as indicated by criteria for entrance into early-intervention programmes.[122] We found no difference in negative symptom outcomes across those studies with a mean patient age ⩽35 years (pooled SMD −0.342, 95% CI −0.528 to −0.156) compared with those with a mean patient age >35 years (pooled SMD −0.284, 95% CI −0.520 to −0.048). We also tested this by comparing outcomes for those receiving SEI (pooled SMD −0.340, 95% CI −0.474 to −0.206) as compared with those treated in other regular services (pooled SMD −0.304, 95% CI −0.467 to −0.141). This also did not reveal any differences in outcome on negative symptoms across the two types of services.

Are there differences in effectiveness of intervention provided in individual v. group format?

An investigation into intervention format revealed no differential effects of group (pooled SMD −0.31, 95% CI −0.601 to −0.019), individual (pooled SMD −0.313, 95% CI −0.505 to −0.120) and combined formats (pooled SMD −0.243, 95% CI −0.483 to −0.004).

Does intensity of interventions have an impact on effectiveness?

As psychotherapy is traditionally offered over 45 to 50 min per week,[123] we used a cut-off of 45 min per week as a measure of high *v.* low intensity of treatment. We found that interventions lasting over 45 min per week were more effective (pooled SMD −0.341, 95% CI −0.558 to −0.125) than those offered over less than 45 min per week (pooled SMD −0.024, 95% CI −0.373 to 0.324).

Why might differences in effect of interventions emerge only when TAU is used as the control condition and not when active controls are used?

The putative mechanisms that might be responsible for the effectiveness of experimental interventions, when compared with TAU as controls, might be similar to those incorporated in some of the active controls used. In order to explore this question, we assigned a putative mechanism of action to each intervention tested based on the content of the intervention: behaviour activation (for example CBT, activity groups, recreation, crafts[124,125]), social engagement (for example supportive therapy, befriending[126]), skill enhancement (for example skills training, occupational therapy, vocational rehabilitation[127]), neurocognitive (for example cognitive remediation, cognitive rehabilitation[128]) and non-specific (for example video games[91]). We found similar effects from experimental interventions and active controls when the latter utilised one of the following mechanisms of action: skill enhancement (pooled SMD 0.206, CI −0.039 to 0.451); behavioural activation (pooled SMD −0.066, 95% CI −0.257 to 0.124); non-specific mechanism of action (pooled SMD −0.068, 95% CI −0.402 to 0.226); social engagement (pooled SMD −0.276, 95% CI −0.608 to 0.056) and neurocognitive (pooled SMD −0.431, 95% CI −1.48 to 0.618).

Publication bias

Results of the funnel plot used to determine publication bias indicate a large grouping of studies left of the mean, suggesting that those studies reporting negative effects may have been less likely to have been published (online Fig. DS1).

Discussion

Main findings

Our meta-analysis and systematic review revealed evidence that negative symptoms can be improved at least modestly with psychosocial and psychological interventions. Although guidelines have traditionally supported the use of CBT, findings from skills-based interventions (SBIs) suggest that the latter are likely to have comparative, if not enhanced utility, as long as the treatment is continued. Although there is some suggestion for the effectiveness of physical activity and music, study quality for these interventions was generally not satisfactory and higher-quality studies are indicated. The largest number of studies was available in support of CBT and SBI. Overall the quality of most studies was medium.

Across study domains, effect sizes of decrease in negative symptoms over time tended to be small. Only SBIs, CBT, music therapy, exercise, body psychotherapy and SEI demonstrated overall moderate effect sizes, largely in comparison with TAU. Neurocognitive, family-based and humour therapies were not found to be an effective treatment for negative symptoms, even compared with TAU.

Across interventions, we found that skill enhancement and behavioural activation were more successful than TAU in targeting negative symptoms in psychosis. This finding has face validity in

that improved skills, and particularly social skills, are likely to be associated with increases in prosocial behaviours (and *vice versa*), that are key indicators of negative symptom improvement. Sensitivity analyses of active control interventions suggest that certain active mechanisms of action are present in both experimental and active controls and, therefore, explain lack of differences in outcome when experimental interventions are compared with active controls. Further, we found that across all experimental interventions, treatment intensity of at least more than 45 min per week is associated with a better outcome. All things being equal, consistency and repetition may partially explain this effect, as may increased social contact. Indeed, we found that group format was as effective as individual format, suggesting some advantages in terms of cost-effectiveness.

Interpretation of our findings

Most studies available for review were not designed to treat negative symptoms and we used data reported on change in negative symptoms irrespective of the primary outcome for the study. As a result, patients were not selected for their negative symptom status. However, notwithstanding differences in rating scales used, our findings from a large number of CBT and SBI studies allowed adequate data comparisons. The results from these suggest that those with higher levels of negative symptoms on entry undergo the greatest negative symptom improvement. This suggests the utility of CBT and SBIs among populations with high levels of negative symptoms. However, few studies selected patients with high levels of negative symptoms.

The quality of evidence from the majority of studies in this review was at best moderate. Many studies used small samples and did not account for attrition, limiting the power of many studies to detect significant results. Larger CBT and SBI studies were somewhat more likely to report a significant effect of the experimental intervention, suggesting a need for studies of other psychosocial and psychological interventions to be designed with adequate power.

Consistency of findings was difficult to establish. We found much evidence of high heterogeneity across studies. Within intervention categories there was great variation with regard to treatment protocol, population, type of control and measurement used. Despite this, our conclusions of somewhat limited evidence for the effectiveness of psychological and psychosocial interventions are perhaps not surprising, given the nature of negative symptoms and the overall prolonged length of illness of study participants. Treatment success is often dependent upon participation, motivation and communication,[129] suggesting that greater levels of negative symptoms may preclude the very outcomes being targeted.[130] That patients were often older, from in-patient settings and chronically ill suggest that they may be struggling from unresolved side-effects from medications, symptoms, social decline and a gradual deterioration of hope that may further challenge treatment outcomes.[130] In contrast, very few studies included in this review were targeted towards those in the earliest phases of psychosis. Although sensitivity analyses did not indicate any marked difference in negative symptom outcomes according to age, some benefit of younger age, likely reflective of an earlier phase in the course of illness, and treatment in an early-intervention service, was suggested from the data. It is of note that we were limited to utilising study reports of mean patient age that most likely included wide variation with general inclusion criteria of patients aged 18 – 60/65. Indeed, the encouraging results of SEI with FEP populations[113,114] confirm the important role of high-quality interventions delivered early on in the course of illness and the role of combined treatments that individually have well-established evidence of efficacy. Further RCTs delivering treatment during this critical period in psychosis may show more promising results.

Limitations

This meta-analysis and review has several other limitations. Given that virtually all patients across studies continued to be prescribed antipsychotic medications, findings regarding the utility of interventions must be examined within this context of drug therapy. We also excluded non-English language studies, although some studies were conducted outside North America or Europe. We were not able to compare monetary as well as other cost benefits of treatment, including adverse effects, that might further indicate increased utility of any one treatment. The only study[29] that examined adverse effects, defined as 'suicides, suicide attempts, suicidal crises, and severe symptom exacerbations over a period of 12 months after inclusion in the study' compared CBT with cognitive remediation in a sample of 198 patients with schizophrenia. They found that although there were adverse events over the course of the trial, the difference between groups was not significant and did not suggest a subgroup of patients who might necessitate additional monitoring. Finally, we were also not able to differentiate between treatment effects on specific domains (expressive *v.* motivational) of negative symptoms as well as on primary *v.* secondary negative symptoms. The latter include depression, and the possible side-effects of continued anti- psychotic medications that may mask as negative symptoms.[131] This disentanglement would allow us to determine to what extent interventions were targeting specific areas of negative symptoms as well as enduring primary *v.* secondary and transient negative symptoms. Future intervention studies designed to target and measure negative symptoms in psychosis as a primary outcome may provide greater clarity as to treatment mechanisms and re- lated outcomes. This would eventually assist in designing more ef- fective psychological and psychosocial interventions for treatment of negative symptoms in future.

Danyael Lutgens, MSc, Department of Psychiatry, McGill University, Douglas Mental Health University Institute, Montre´ al, Quebec; Genevieve Gariepy, PhD, McGill University, Institute for Health and Social Policy, Montre´ al, Quebec; Ashok Malla, MD, FRCPC, McGill University, Douglas Mental Health University Institute, Montre´ al, Quebec, Canada

Correspondence: Ashok Malla, Department of Psychiatry, Douglas Mental Health University Institute, ACCESS-Canada Pavilion, 6625 LaSalle Boulevard, Montre´ al, Quebec, H4H 1R3, Canada. Email: ashok.malla@mcgill.ca

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EXTRA CONTENT ONLINE

Data supplement to Lutgens et al. Psychological and psychosocial interventions for negative symptoms in psychosis: systematic review and meta-analysis**.** Br J Psychiatry doi: 10.1192/bjp.bp.116.197103

Online supplement DS1

Key search terms:

(Psychotic Disorders OR psychotic OR psychosis OR psychoses OR schizoaffective OR schizophreniform OR Schizophrenia OR schizophrenia OR schizophrenias OR schizophrenic OR "delusional disorder" OR "delusional disorders" OR "deficit syndrome") AND ("negative symptom" OR "negative symptoms" OR "negative symptomatology" OR "negative symptomatologies" OR "negative syndrome" OR "negative syndromes" OR "Alogia" OR "affective blunting" OR "blunted affect" OR "affective flattening" OR "flat affect" OR "inappropriate affect" OR "restricted affect" OR affectiveness OR affectivity OR "Anhedonia" OR Anhedonia OR anhedonic OR Avolition OR avolitional OR Amotivation OR amotivational OR "Apathy" OR Apathy OR apathetic OR Asocial OR asociality) AND (randomized controlled trial OR controlled clinical trial OR randomized OR randomised OR placebo OR clinical trials as topic OR randomly OR trial)

Example of search strategy for Pubmed:

((((Psychotic Disorders[MeSH] OR psychotic[tw] OR psychosis[tw] OR psychoses[tw] OR schizoaffective[tw] OR schizophreniform[tw] OR Schizophrenia[MeSH] OR schizophrenia[tw] OR schizophrenias[tw] OR schizophrenic[tw] OR "delusional disorder"[tw] OR "delusional disorders"[tw] OR "deficit syndrome"[tw]))) AND (("negative symptom"[tw] OR "negative symptoms"[tw] OR "negative symptomatology"[tw] OR "negative symptomatologies"[tw] OR "negative syndrome"[tw] OR "negative syndromes"[tw] OR "Alogia"[tw] OR "affective blunting"[tw] OR "blunted affect"[tw] OR "affective flattening"[tw] OR "flat affect"[tw] OR "inappropriate affect"[tw] OR "restricted affect"[tw] OR affectiveness[tw] OR affectivity[tw] OR "Anhedonia"[Mesh] OR Anhedonia[tw] OR anhedonic[tw] OR Avolition[tw] OR avolitional[tw] OR Amotivation[tw] OR amotivational[tw] OR "Apathy"[Mesh] OR Apathy[tw] OR apathetic[tw] OR Asocial[tw] OR asociality[tw]))) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans[mh]))

Table DS1 Pooled SMD by study characteristics

Active control only						
Study characteristic	**# of studies**	**Pooled SMD**	**Lower 95% CI**	**Upper 95% CI**	**I^2**	**p-value of I^2**
Mechanism						
Nonspecific	3	-0.068	-0.402	0.266	0.0%	0.706
Behaviour activation	9	-0.066	-0.257	0.124	23.5%	0.234
Social Engagement	10	-0.276	-0.608	0.056	83.4%	0.000
Skill enhancement	3	0.206	-0.039	0.451	0.0%	0.712
Neurocognitive	2	-0.431	-1.48	0.618	75.3%	0.044

All studies						
Study characteristic	**# of studies**	**Pooled SMD**	**Lower 95% CI**	**Upper 95% CI**	**I^2**	**p-value of I^2**
Mean age of sample						
≤ 35 years old	27	-0.347	-0.553	-0.141	81.4%	0.001
> 35 years old	31	-0.284	-0.520	-0.048	86.5%	0.019
Type of sample						
FEP	6	-0.331	-0.542	-0.120	21.3%	0.274
General population	57	-0.304	-0.467	-0.141	85.0%	0.000
Elderly	1	-0.414	-0.707	-0.121	-	-
Format						
Group	23	-0.31	-0.601	-0.019	88.5%	0.000
Combined	6	-0.243	-0.483	-0.004	80.4%	0.000
Individual	34	-0.313	-0.505	-0.120	64.9%	0.014
Intensity of intervention						
≥45 min/week	39	-0.341	-0.558	-0.125	87.3%	0.000
< 45 min/week	6	-0.024	-0.373	0.324	60.2%	0.028
Type of intervention						
CBT	16	-0.336	-0.548	-0.124	73.60%	0.000
ST, OT, and CAT	13	-0.438	-0.775	-0.102	85.80%	0.000
NCT	14	-0.15	-0.408	0.108	74.20%	0.000
Exercise Therapy	7	-0.358	-0.705	-0.010	54.80%	0.039
Art and Music Therapy	7	-0.139	-0.779	0.502	94.90%	0.000
Family Based Intervention	3	-0.177	-0.698	0.344	65.40%	0.056
Misc.	7	-0.400	-0.636	-0.164	33.30%	0.174

Table DS2 Cognitive–behavioural therapy

Study characteristics									Study results at treatment end		
Reference	Intervention	Control	Treatment duration in months (max sessions offered)	Duration of follow-up (months)	Assessment instrument	Diagnosis/ status	% Male	*n*	Exp. *v.* TAU, SMD (95% CI)	Exp. *v.* Control, SMD (95% CI)	Quality
Barrowclough *et al* (2006)[35]	CBT (group)	TAU	6 (18)	12	PANSS Neg	SZ, SA/NA	NR	113 (CBT=57, TAU=56)	–0.06 (–0.43 to 0.31)	NA	Medium
Cather *et al* (2005)[36]	CBTf	Psychoed programme	4 (16)	NA	PANSS PSYRATS	SZ, SA/out-patients	57%	30 (CBT=16, AC=12)	NA	–0.01 (–0.75, 0.73)	High
Drury *et al* (1996), [37] (2000)[38]	CT (group and individual)	Social recreation and support	6 (128)	9, 60	PAS – flat affect, poverty of speech	PD non-specific/in-patients	62%	40 (CT=20, AC=20)	NA	NR, missing data	Medium
Farhall *et al* (2009)[24]	CBTp	TAU	9–12 (24)	18	PANSS Neg	SZ, SA, DD, MD/out-patients	59%	94 (CBT=45, TAU=49)	0.30 (–0.11 to 0.71)	NA	Medium
Granholm *et al* (2014)[25]	CBT SST (group)	Active goal focused supportive contact	9 (36 + 12 booster)	21	SANS – diminished expression and motivation factors	SZ, SA/out-patients	66%	149 (CBT SST=73, AC=76)	NA	–0.23 (–0.56 to 0.09)	High
Grant *et al* (2012)[39]	CT	TAU	18 (72)	NA	SANS	SZ, SA/ chronic low functioning	67%	60 (CT=31, TAU=29)	Avolition Apathy Subscale, t_{145}=2.20, *P*=0.01*	NA	High
Gumley *et al* (2003)[26]	CBT	TAU	12 (range 2–16)	NA	PANSS Neg	SZ, SA/out-patients	72%	144 (CBT=72, TAU=72)	–0.35 (–0.68 to –0.02) *	NA	Medium
Hall & Tarrier (2003)[40]	CBT	TAU	1.75 (7)	3	PANSS Neg	PD/in-patients	67%	25 (CBT=13, TAU=12)	–1.77 (–2.71 to –0.83) *	NA	Medium
Jackson *et al* (2008)[27]	CT	Befriending	3.5 (20)	12	SANS	FEP – acute phase	73%	62 (CT= 31, AC=31)	NA	–0.45 (–0.95 to 0.06)	High
Klingberg *et al* (2011)[29]	CBT	Cognitive remediation	9 (20)	NA	PANSS Neg	SZ/out-patients	56%	198 (CBT=99, AC=99)	NA	0.00 (–0.28 to 0.28)	High
Klingberg *et al* (2010)[28]	CBT (group)	TAU	8 (40 + 4 with family in hospital; 8 in community + as needed)	NA	PANSS Neg –	SZ, SA/in-patient in transition to out-patient	48%	169 (CBT=84, TAU=85)	NR, *P*=0.014*	NA	Medium
Krakvik *et al* (2013)[41]	CBTp	TAU (+ waitlist)	6 (20)	12	SANS	SZ, SA, DD/ in- and out-patients	52%	45 (CBT=23, TAU=22)	–0.54 (–1.13 to 0.06)	NA	Medium
Leclerc *et al* (2000)[42]	CBT (group)	TAU	3 (24)	6	PANSS Neg	SZ, SA, PP/ out- and in-patients	73%	99 (CBT=55, TAU=44)	NR, missing data	NA	Medium
Lecomte *et al* (2012),[43] (2008)[44]	CBT (group)	Skills training (Group), (TAU + Waitlist)	3 (24)	15	BPRS neg	FEP – Sz spectrum, MDP, Pnos/out-patients	74%	129 (CBT=48, AC=54, TAU=27)	t_{12}=–2.00, *P*=0.006	NR, missing data	High
Li *et al* (2015)[45]	CBT (culturally adapted)	Supportive Therapy	6 (15)	15	PANSS Neg	Out-patients	37%	192 (CBT=96, AC=96)	NA	–0.17 (–0.45 to 0.12)	High
Lincoln *et al* (2012)[46]	CBTp	TAU (+ waitlist)	4–5 (45)	12	PANSS Neg	SZ, SA, DD, BPD/ out-patients	57%	80 (CBTp=40, TAU=40)	0.11 (–0.34 to 0.55)	NA	Medium

Morrison *et al* (2014)[30]	CT	TAU	18 (26 + 4 booster)	NA	PANSS Neg	SZ, SA, DD/ FEP out-patients	53%	74 (CT=37, TAU=37)	NA	–0.79 (–1.27 to –0.32)*	High
Naeem *et al* (2015)[47]	CBTp (culturally adapted)	TAU	4 (4 with caregiver + 1 with family)	NA	PANSS Neg	SZ – or related disorder/out-patients	60%	116 (CBTp=59, TAU=57)	NR, *P*<0.001*	NA	Medium
Peters *et al* (2010)[48]	CBTp	TAU (+ waitlist)	6 (mean of 16)	3	PANSS Neg	PD – diagnoses not defined/ out-patients	60%	74 (CBTp=36, TAU=38)	–0.31 (–0.76 to 0.15)	NA	Medium
Rector *et al* (2003)[49]	CBT	TAU	6 (20)	6	PANSS Neg	SZ, SA/ out-patients	45%	42 (CBT=24, TAU=18)	–0.50 (–1.12 to 0.12)	NA	Medium
Sensky *et al* (2000)[31] Turkington *et al* (2008)[54]	CBT	Befriending	9 (19)	9, 60	SANS	SZ/out-patients	58%	90 (CBT=46, AC=44)	NA	NR, missing data	High
Startup *et al* (2005)[50]	CBT	TAU	6 (24)	12, 24	SANS	SZ, SP, SA/ out-patients	75%	90 (CBT=47, TAU=43)	–0.64 (–1.06 to –0.21)*	NA	Medium
Tarrier *et al* (2004)[51]	CBT	Supportive counselling, TAU	3 (20)	18	PANSS Neg	SZ, SA, SP, DD, Pnos/ in-patients	68%	316 (CBT= 101, AC=106, TAU =102)	–0.94 (–1.22 to –0.65)* (Liverpool)	0.24 (–0.03 to 0.51) (Liverpool)	High
Tarrier *et al* (2000)[52]	CBT	Supportive counselling / TAU	3 (20 + 4 booster sessions)	24	SANS	SZ, SA, DD/ out- and in-patients	79%	87 (NR)	$F(2,56)=5.55$, $P=0.03$*	NR, missing data	Medium
Turkington *et al* (2006),[32] Turkington & Kingdon (2000)[33] Malik *et al* (2009)[34]	CBT – brief	TAU	2–3 (6 + 3 for main caregiver)	12, 24	NSRS	SZ/in- and out-patients	NR	422 (NR)	NR, *P*=0.002* (apathy, reduced volition and asociality items only)	NA	Medium
Valmaggia *et al* (2005)[53]	CBT	Supportive counselling plus psycho-education	5.5 (16)	6	PANSS Neg	SZ/in-patients	71%	58 (CBT=35, AC=23)	NA	0.37 (–0.16 to 0.90)	High

See end of Table DS8 for footnotes for all tables.

Table DS3 Skills-based therapies

Study characteristics									Study results at treatment end		
Reference	Intervention	Control	Treatment duration in months (max sessions offered)	Duration of follow-up (months)	Assessment instrument	Diagnosis/ status	% Male	*n*	Exp. *v.* TAU, SMD (95% CI)	Exp. *v.* Control, SMD (95% CI)	Quality
Bartels *et al* (2014)[55]	Skills training (group and individual)	TAU	24 (1st year=52, 24 field trips, 12 individual/ 2nd year=12 sessions)	12	SANS	SZ, SA, BP, MD/ out-patients	42%	183 (ST=90, TAU=93)	–0.41 (–0.71 to –0.12) *	NA	High
Bio & Gattaz *al* (2011)[71]	Vocational rehabilitation	TAU (+ waitlist)	6 (NR)	NA	PANSS Neg	SZ/out-patients	79%	102 (VR=57, TAU =55)	–0.18 (–0.55 to 0.19)	NA	Medium
Cook *et al* (2009)[66]	Occupational therapy (individual + family)	TAU	12 (Individually tailored)	NA	SANS	SZ, psychosis/ NA	66%	44 (OT=30, TAU=14)	NR, missing data	NA	Medium
Dobson *et al* (1995)[61]	Social skills training (group)	Social Milieu	2.25 (36)	3, 6	PANSS Neg	SZ/out-patients (day hospital)	71%	45 (NR: SS=15, SM=13 – treatment completers only)	NA	*F*=5.73, d.f.=1,26, *P* <0.006 * (emotional withdrawal, rapport and speech items)	Medium
Foruzandeh *et al* (2013)[68]	Occupational therapy	TAU	6 (3 hours a day, 6 days a week)	NA	SANS	SZ/in-patients	72%	60 (OT=30, TAU=30)	–2.90 (–3.63 to –2.17) *	NA	Medium
Hansen *et al* (2012)[69]	Cognitive adaptation training	TAU	6 (12)	9	PANSS Neg	SSD/out-patients	65.00%	62 (CAT=31, TAU=31)	–0.08 (–0.58 to 0.42)	NA	High
Hayes *et al* (1995)[59]	Social skills training (group)	Discussion group	10 (36 + 9 booster)	NA	SANS	SZ/out-patients	NR	63 (NR)	NA	*F*=1.5, d.f.=2.31, *P*<0.1*	Medium
Horan *et al* (2010)[58]	Social cognitive skills training (group)	Illness self-management and relapse prevention skills training	1.5 (12)	NA	BPRS Anergia	SZ, SA/ out-patients	72%	34 (NR: SC=15, ISM=16 – treatment completers only)	NA	0.28 (–0.03 to 0.58)	Low
Li & Wang (1994)[60]	Skills training	TAU	3 (18)	NA	SANS – Chinese version	SZ/in-patients	54%	52 (ST=28, TAU=24)	–0.92 (–1.49 to –0.35) *	NA	Low
Lin *et al* (2013)[63]	IMR programme (group)	TAU	.75 (6)	1	BPRS Neg subscale: thought disturbance, anergia, affect, and disorganisation	SZ, SA/in-patients	64%	94 (IMR=48, TAU=49)	–0.15 (–0.54 to 0.25) (anergia subscale)	NA	Medium
Quee *et al* (2014)[70]	Cognitive adaptation training	TAU (+ waitlist)	8 (32)	NA	NSA–M	SZ, SA, Pdnos/in- and out-patients	80%	36 (CAT=16, TAU=14: randomisation data only available for *n*=30)	NR, missing data	NA	Low

Roberts *et al* (2014)[57]	Social cognition and interaction training (group)	TAU	6 (20–24)	9	PANSS Neg	SZ, SA/out-patients	67%	66 (SCIT=33, TAU=33)	–0.13 (–0.61 to 0.35)	NA	Medium
Rus-Calafell *et al* (2013)[65]	Social skills training (group)	TAU	2 (16)	6	PANSS Neg	SZ, SA/ out-patients	78.00%	36 (SST=18, TAU=18)	–0.39 (–1.05 to 0.27)	NA	Medium
Gil-Sanz *et al* (2009)[64]	Social cognition training (group)	TAU	2.5 (20)	NA	PANSS Neg	SZ/out-patients	50%	14 (SC=7, TAU=7)	–0.18 (–1.23 to 0.87)	NA	Low
Tatsumi *et al* (2011)[67]	Occupational therapy	TAU	3.75 (15)	NA	SANS	SZ/in-patients	53%	38 (OT=19, TAU=19)	NR, missing data *	NA	Medium
Valencia *et al* (2007)[56]	Psychosocial skills training (group + family)	TAU	12 (48)	NA	PANSS Neg	SZ/out-patients	64%	98 (PST=49, TAU=49)	–0.82 (–1.24 to –0.41) *	NA	High
Xiang *et al* (2006)[62]	Social skills training (group)	Supportive counselling	2 (16)	6	PANSS Neg	SZ/out-patients	47%	96 (SST=48, SC=48)	NA	–0.66 (–1.07 to –0.25)*	Medium

See end of Table DS8 for footnotes for all tables.

Table DS4 Neurocognitive therapies

Study characteristics									Study results at treatment end		
Reference	Intervention	Control	Treatment duration in months (max sessions offered)	Duration of follow-up (months)	Assessment instrument	Diagnosis /status	% Male	*n*	Exp. *v.* TAU, SMD (95% CI)	Exp. *v.* Control, SMD (95% CI)	Quality
Ahmed *et al* (2015)[81]	Cognitive remediation (computer assisted)	Computer games	5 (60)	NA	PANSS Neg	SZ/in-patient (forensic)	87%	78 (CR=42, AC=36)	NA	–0.19 (–0.63 to 0.26)	High
Bellucci *et al* (2003)[82]	Cognitive rehabilitation (computer assisted)	TAU	2 (18)	NA	SANS	SZ, SA/ out-patients	47%	34 (CRhab=17, TAU=17)	–0.57 (–1.26 to 0.12)	NA	Medium
Cella *et al* (2014)[73]	Cognitive remediation	TAU	3.5 (40)	NA	PANSS Neg (5 factor structure)	SZ/out-patients	73%	85 (CR=43, TAU=42)	0.02 (–0.40 to 0.45)	NA	Low
Eack *et al* (2013)[86]	Cognitive enhancement (group)	Supportive therapy	24 (45)	NA	The Wing Negative Symptom Scale and BPRS	SZ, SA (early course)/ out-patients	69%	58 (CE=31, AC=27)	NA	$t(82)=2.63$, $P=0.01$*	Medium
Farreny *et al* (2012)[72]	Cognitive remediation (group)	Leisure Activities	4 (32)	10	PANSS Neg	SZ, SA/ out-patients	68%	62 (CR= 34, AC= 28)	NA	–0.19 (–0.70 to 0.31)	Medium
Gharaeipour & Scott (2012)[76]	Cognitive remediation (group)	Supportive therapy	2 (48)	NA	PANSS Neg	SZ/in-patients	71%	42 (CR=21, AC=21)	NA	–1.83 (–2.55 to –1.10) *	High
Holzer *et al* (2013)[80]	Cognitive remediation (computer assisted)	Computer games	2 (16)	NA	PANSS Neg	PD/ adolescent out-patients	57%	32 (CR=18, AC=14)	NA	0.15 (–0.55 to 0.85)	Medium
Mueller *et al* (2015)[85]	Neurocognitive therapy	TAU	3.75 (30)	9	PANSS Neg	SZ, SA (FEP)/out-patients	69%	156 (NT=81, TAU=75)	0.65 (0.33 to 0.97)*	NA	High
Nemoto *et al* (2009)[83]	Cognitive training for divergent thinking	Program for convergent thinking	2 (independent homework for 15 minutes, 6 days a week)	NA	PANSS Neg	SZ/out-patients	53%	17 (CTDiv= 9, AC=8)	NA	–1.10 (–2.13 to –0.07)*	Medium
Ostergaard *et al* (2014)[77]	Cognitive remediation	TAU	4 (38)	12	PANSS Neg	FEP/out-patients	54%	117 (CR=60, TAU=57)	–0.05 (–0.41, 0.31)	NA	High
Penades *et al* (2006)[74]	Cognitive remediation (group)	CBT	4 (40)	6	PANSS Neg	SZ/out-patients	57%	40 (CR =20, AC=20)	NA	–0.11 (–0.73 to 0.51)	Medium
Sanchez *et al* (2014)[75]	Cognitive remediation (group)	Group activities	3 (36)	NA	PANSS Neg	SZ/in-patients	76%	92 (CR =38, TAU= 54)	NA	–0.09 (–0.51 to 0.32)	Medium
Tan *et al* (2015)[79]	Cognitive remediation	Musical and dancing therapy (MDT)	2.5 (40)	NA	PANSS Neg	SZ/in-patients	53%	104 (CR=52, TAU=52)	NA	0.19 (–0.20 to 0.57)	Medium
Twamley *et al* (2012)[84]	Compensatory cognitive training (group)	TAU	3 (24)	3	PANSS Neg	SZ, SA, PMD, PDnos/	65%	69 (CCT=38, TAU=31)	NR, $P<0.025$ *	NA	Medium

						out-patients					
Vauth *et al* (2005)[87]	CBT groups: cognitive training *v.* self-management skills for negative symptoms	TAU	2 (8)	12	PANSS Neg	SZ/in-patient	64	138 (CogT=47, SMS=45, VRA=46)	–0.15 (–0.56 to 0.26)	–0.23 (–0.64 to 0.18)	Medium
Vita *et al* (2011)[78]	Computer assisted cognitive remediation/ integrated psychological therapy (group)	Non-cognitive oriented rehab	6 (48)	NA	PANSS Neg	SZ/NR	69%	84 (CR=26, AC=30, TAU=28)	0.10 (–0.43 to 0.62)	0.73 (0.18 to 1.27)*	Medium

See end of Table DS8 for footnotes for all tables.

Table DS5 Exercise-based therapies

Study characteristics									Study results at treatment end		
Reference	Intervention	Control	Treatment duration in months (max sessions offered)	Duration of follow-up (months)	Assessment instrument	Diagnosis/status	% Male	*n*	Exp. *v.* TAU, SMD (95% CI)	Exp. *v.* Control, SMD (95% CI)	Quality
Acil *et al* (2008)[91]	Exercise (group)	TAU	2.5 (30)	NA	SANS	SZ/in-patients transferring to out-patients	60%	30 (EX=15, TAU =15)	–1.25 (–2.03 to –0.46)* (except alogia subscale)	NA	Low
Cassilhas *et al* (2015)[97]	Resistance training (group)	Concurrent exercise, training w/o weights	5 (40)	NA	PANSS Neg	SZ/NR	100%	47 (RESEX=14, CONCEX=17, AC=16)	–1.02 (–1.94 to –0.10)*	–0.38 (–1.25 to 0.50)	High
Ho *et al* (2012)[88]	Tai Chi (group)	TAU (+waitlist)	1.5 (12 full + 12 half)	1.5	SANS	SZ/in-patients	40%	30 (Tai Chi=15, TAU=15)	–0.63 (–1.36 to 0.11)	NA	Medium
Ikai *et al* (2014)[89]	Yoga (group)	TAU	2 (8)	2 (NO)	PANSS Neg	SZ and related disorders /out-patients	66%	50 (Yoga= 25, TAU=25)	–0.13 (–0.69 to 0.42)	NA	High
Kaltsatou *et al* (2015)[96]	Traditional dance (group)	TAU	8 (24)	NA	PANSS Neg	SZ/in-patients	81%	31 (TD=16, TAU=15)	–0.05 (–0.76 to 0.65)	NR, missing data	High
Loh *et al* (2015)[95]	Structured walking (group)	TAU	3 (36)	NA	PANSS Neg	SZ/in-patients	71%	104 (SW=52, TAU=52)	NR, missing data*	NA	Low
Manjunath *et al* (2013)[92]	Yoga (group and individual)	Exercise	0.5 (14 + at home practice)	1	PANSS Neg	Non AP/ in-patients	55%	88 (yoga=44, AC=44)	NA	–0.12 (–0.54 to 0.29)	Low
Scheewe *et al* (2013)[93]	Exercise (group)	Occupational therapy	6 (48)	NA	PANSS Neg	SZ, SA/ NR	73%	63 (EX=31, AC= 32)	NA	0.11 (–0.38 to 0.61) (per protocol)	Medium
Varambally *et al* (2012)[96]	Yoga (group and individual)	Exercise, TAU waitlist	1 (25) + 3 ('regular' home practice)	NA	PANSS Neg	SZ/out-patients	71%	120 (Yoga=47, AC=37, TAU =36)	NR, NA missing data*	NR, NA missing data*	Medium
Visceglia *et al* (2011)[90]	Yoga (group)	TAU	2 (16)	NA	PANSS Neg	SZ/in-patients	67%	18 (yoga=10, TAU=8)	t=– 3.04, $P<0.01$*	NA	Low

See end of Table DS8 for footnotes for all tables.

Table DS6 Arts therapies

Study characteristics									Study results at treatment end		
Reference	Intervention	Control	Treatment duration in months (max sessions offered)	Duration of follow-up (months)	Assessment instrument	Diagnosis / status	% Male	*n*	Exp. *v.* TAU, SMD (95% CI)	Exp. *v.* Control, SMD (95% CI)	Quality
Crawford *et al* (2012)[98]	Art therapy (group)	Activity groups, TAU	9–12 (39–52)	24	PANSS Neg	SZ/out-patients	67%	417 (Art=140, AC=140, TAU=137)	0.14 (–0.09 to 0.38)	1.30 (1.04 to 1.56)	High
Gold *et al* (2013)[101]	Music therapy	TAU	3 (18–26)	NA	SANS	PD, AD, Other mental disorders/ in-patients and out-patients	52%	144 (Music=72, TAU=72)	NR, *P*<0.001 (per protocol)*, NR, *P*=0.018 (ITT) *	NA	Medium
Lu *et al* (2013)[104]	Music therapy (group)	TAU	1.25 (10)	3	PANSS Neg	SZ/in-patients	74%	80 (Music=40, TAU=40)	–0.51 (–0.96 to –0.07)*	NA	High
Montag *et al* (2014)[99]	Art therapy (group)	TAU	1.5 (12)	3	SANS	SZ/in-patients	63%	58 (AT=29, TAU=29)	–0.24 (–0.76 to 0.28)	NA	High
Talwar *et al* (2006)[100]	Music therapy	TAU	3 (12)	NA	PANSS Neg	SZ,SS/ in-patients	73%	81 (33=Music, 48=TAU)	–0.30 (–0.74 to 0.15)	NA	High
Tang *et al* (1994)[103]	Music therapy (group)	TAU	1 (19)	NA	SANS, DAS	SZ, SA, PD, other mental disorders/ in-patients	NR	76 (Music=38, TAU=38)	–1.08 (–1.56 to –0.60)*	NA	Medium
Ulrich *et al* (2007)[102]	Music therapy (group)	TAU	8 (mean=7.5)	NA	SANS	SZ, SA, DD, (ICD-10 code F20–F29)/In-patients	54%	37 (Music =21, TAU=16)	–0.40 (–1.06 to 0.25)	NA	Medium

See end of Table DS8 for footnotes for all tables.

Table DS7 Family-based therapies

Study characteristics									Study results at treatment end		
Reference	Intervention	Control	Treatment duration in months (max sessions offered)	Duration of follow-up (months)	Assessment instrument	Diagnosis /status	% Male	*n*	Exp. *v.* TAU, SMD (95% CI)	Exp. *v.* Control, SMD (95% CI)	Quality
Bradley *et al* (2006)[105]	Multiple family intervention (individual family and group)	TAU	12 (3 individual families + 24 group)	NA	SANS	SZ, SA, SP/out-patients	30%	59 family pairs (FBT=25, TAU=25)	0.38 (–0.18 to 0.94)	NA	Medium
Buchkremer *et al* (1997)[109]	Multiple family psychoeducation and psychotherapy (patients only and family groups)	Leisure Time group	12 (psychoeducational medication training=10; cognitive psychotherapy=15; key person counselling; Leisure time=NR)	24	SANS	SZ/out-patients	58%	191 patients (Group 1 (PMT, LTG)=32, Group 2 (PMT LTG KC)=35, Group 3 (PMT, CP)=34, Group 4 (PMT, CP, KC)=33, Group 5 (LTG)=57.	NR, *U*-test, p=0.91	NR, *U*-test, *P*=0.91	Medium
Cai *et al* (2015)[110]	Family therapy (individual)	TAU	2.5 (10 sessions)	18	PANSS Neg	SZ/out-patient	46%	256 (FBT=133, TAU, 123)	0.13 (–0.11 to 0.38)	NA	Medium
Calvo *et al* (2014.)[108]	Family psychoeducational intervention (individual and group)	Unstructured groups	9 (3 individual and 12 group sessions)	NA	PANSS Neg	SZ, SA, SP, BP with PF, BPD, Pnos/ adolescents with early onset/ out-patients	62%	55 (FBT=27, AC=28)	NA	- 0.42 (–0.95 to 0.12)	High
Dyck *et al* (2000)[107]	Multiple family psychoeducation (group)	TAU	12 (3 family only and approximately 20 group sessions)	NA	SANS, attention removed	SZ, SA/ out-patients	46%	63 (FBT=32, TAU=31)	–0.46 (–0.96 to 0.04)	NA	Medium
Wang *et al* (2013)[106]	Psychosocial rehabilitation – (group)	TAU	18 (18)	NA	PANSS Neg	SZ/out-patients	39%	140 (FBT=30, TAU=50) (at treatment end)	NR, *P*=0.003*	NA	Low

Table DS8 *Miscellaneous therapies*

Study characteristics									Study results at treatment end		
Reference	Intervention	Control	Treatment duration in months (max sessions offered)	Duration of follow-up (months)	Assessment instrument	Diagnosis /status	% Male	*n*	Exp. *v.* TAU, SMD (95% CI)	Exp. *v.* Control, SMD (95% CI)	Quality
Anderson *et al* (2010)[118]	Adherence Therapy (Individual)	TAU	2 (8)	NA	PANSS Neg	SZ/out-patients	78%	26 (AT=12, TAU =14)	NR	NA	Medium
Cai *et al* (2014)[111]	Humour therapy (group)	Handiwork	1.5 (10)	NA	PANSS Neg	in-patient	53%	30 (Humour=15, AC=15)	NA	–0.14 (–0.86 to 0.57)	Low
Choi & Medalia (2010)[120]	Motivational learning (group)	Cognitive tasks	1 (10)	NA	BPRS Neg	SZ, SA/ out-patients	67%	57 (ML=29, AC=28)	NA	NR, *P*=0.08	Low
Garety *et al* (2006)[114]	Specialised early intervention (group and individual)	TAU	1.5 (NA)	NA	PANSS Neg	FEP/out-patients	65%	144 (SEI=71, TAU=73)	–0.55 (–0.88 to –0.22)*	NA	Medium
Gelkopf *et al* (2006)[112]	Humorous movies (group)	Movies (only 15% humorous)	3 (60 movies, each night, 5 nights a week)	NA	PANSS Neg	SZ/in-patients	60%	29 (Humour=15, AC= 14)	NA	0.02 (–0.71 to 0.75)	Low
Gholipour *et al* (2012)[119]	Token therapy	Exercise, TAU	3 (36)	NA	SANS	SZ/in-patients	NR	45 (Token=15, AC=15, TAU=15)	–0.91 (–1.66 to –0.15) *	–0.27 (–0.99 to 0.45)	Low
Rohricht & Priebe (2006)[116]	Body psychotherapy (group)	Supportive counselling	1.5 (20)	4	PANSS Neg	SZ/out-patients	49%	45 (BPT =24, AC =21)	NA	–0.74 (–1.35 to –0.13)	Medium
Thorup *et al* (2005)[113]	Specialised early intervention (group and individual)	TAU	24 (NA)	36	PANSS Neg	FEP/out-patients	59%	547 (SEI=275, TAU=272)	NR, missing data*	NA	Medium
Villalta-Gil *et al* (2009)[117]	Dog-assisted therapy (+ integrated psychological treatment – group)	TAU	3 (25)	NA	PANSS Neg	SZ/in-patients	85%	21 (DAT=12, TAU=9)	NA	0.48 (–0.40 to 1.36)	Low
White *et al* (2011)[115]	Acceptance and commitment therapy	TAU	3 (10)	NA	PANSS Neg	PD/in and out-patients	78%	23 (ACT=13, TAU=14)	–0.42 (–1.19 to 0.34)	NA	High

AC, active control; ACT, acceptance and commitment therapy; BP, brief psychosis; BPD, brief psychotic disorder; BPRS, brief psychiatric rating scale; BPT, body psychotherapy; CAT, cognitive adaptation training; CBT, cognitive–behavioural therapy; CBTp, CBT for psychosis; CBT SST, CBT and social skills training; CBTf, CBT for functioning; CCT, compensatory cognitive training; CE, cognitive enhancement; CogT, cognitive training; CONCEX, concurrent exercise; CP, cognitive psychotherapy; CR, cognitive remediation; CRhab, cognitive rehabilitation; CT, cognitive therapy; CTDiv, cognitive training; DAT, dog-assisted therapy; DAS, disability assessment schedule; DD, delusional disorder; EX, exercise; Exp., experimental intervention; FEP, first-episode psychosis; FBT, family-based therapy; IMR, illness management and recovery programme; ITT, intention-to-treat analysis; KC, key person counselling; LTG, leisure time group; MD, mood disorder; MDP, mood disorder with psychotic features;

ML, motivational learning; NA, not applicable; NR, not reported; NSA-M, negative symptom assessment motivation subscale; NSRS, Negative Symptom Rating Scale; NT, neurocognitive therapy; OT, occupational therapy; PANSS, Positive and Negative Syndrome Scale (neg, negative subscale); PAS, Psychiatric Assessment Scale; PD, psychotic disorder; PF, psychotic features; PMD, psychotic mood disorder; PMT, psychoeducational medication training; Pnos, psychosis not otherwise specified; PP, paranoid psychosis; PST, psychosocial skills; Psychoed, psychoeducation; PsycRehab, psychological rehabilitation; PSYRATS, Psychotic Rating Scales; RESEX, resistance training; SA, schizoaffective disorder; SANS, Scale for Assessment of Negative Symptoms; SC, social cognition; SCIT, social cognition and interaction training; SEI, specialised early intervention; SMS, self-management skills for negative symptoms; SP, schizophreniform; SST, social skills training; ST, skills training; SW, structured walking; SZ, schizophrenia; TAU, treatment as usual; TD, traditional dance; VR, vocational rehabilitation; VRA, vocational remediation. *Denotes significance (*P*-value and statistic reported when data to calculate 95% CI unavailable).

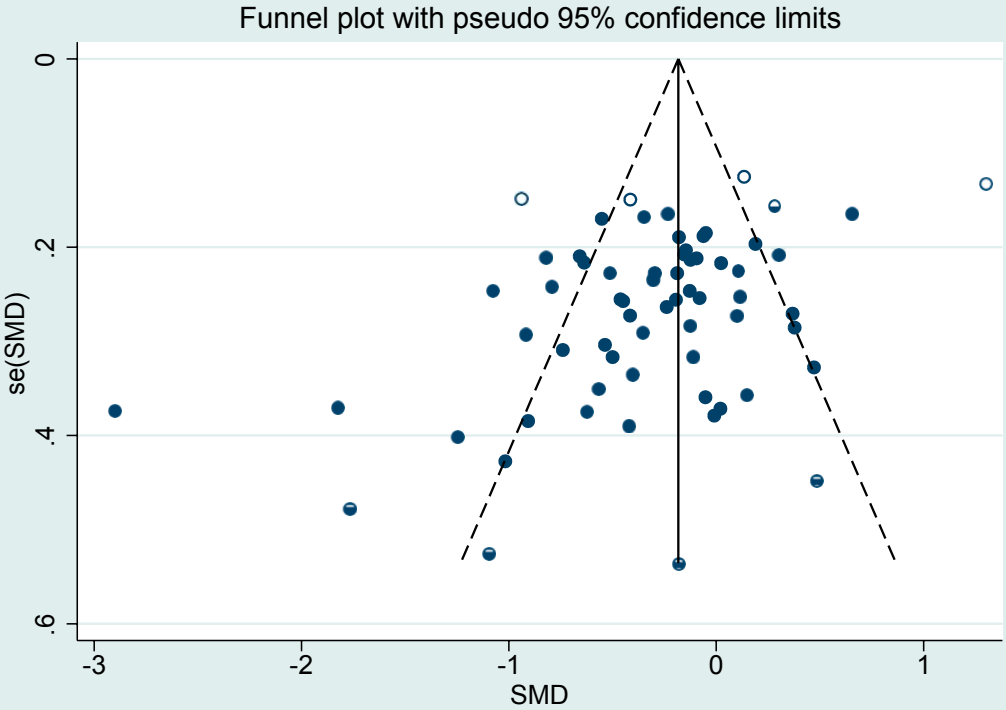
Funnel plot with pseudo 95% confidence limits
se(SMD)
0
.2
.4
.6
-3
-2
-1
0
1
SMD

Fig. DS1

Psychological and psychosocial interventions for negative symptoms in psychosis: systematic review and meta-analysis

Dánya Lutgens, Geneviève Gariepy and Ashok Malla

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Chapter 4: First Episode Psychosis, the critical period and specialized early intervention

4.1 General Introduction

Results from the systematic review and meta-analysis suggest a paucity of highly effective psychological and psychosocial interventions for treating negative symptoms in psychosis. Those that are effective, are at best, moderately so. Notwithstanding this, we found that the package of treatments offered within EI, and that include intensive case management, has a particularly significant impact on negative symptoms in patients who are in the early phase of psychotic disorders, otherwise referred to as first episode psychosis (FEP).

4.2 What is a First Episode of Psychosis?

A FEP is defined as an onset of the first acute psychotic symptom (first-rank) (Larsen, McGlashan, and Moe 1996; Keshavan and Schooler 1992). The first 5 years of FEP are considered a "critical period" for EI (Birchwood, Todd, and Jackson 1998). While EI services may use more or less stringent criteria for FEP status (including age restrictions), entry into such programs is often contingent upon having received either no or minimal prior antipsychotic medication (Malla et al. 2007).

4.3 Consequences of a First Episode of Psychosis

As the first episode of psychosis is most likely to emerge in late to early adolescence (Angermeyer and Kühnz 1988; Faraone et al. 1994), it tends to disrupt social, educational and vocational pathways (Tarrier et al. 2007). Many young people with a FEP live at home with family members who have little knowledge about the illness and who are challenged to provide

support (Merinder et al. 1999). Those with FEP must often learn to navigate through the healthcare system alone (Addington et al., 2002). Often, there are long delays before attaining appropriate care (Anderson et al. 2013; Anderson et al. 2014; Singh and Grange 2006). Indeed, a meta-analysis published in 2005 with 25 studies reported a mean DUP of 103 weeks (Marshall et al. 2005).

For many, a FEP may be preceded by many years of pre-prodromal and prodromal signs and symptoms including anxiety, and sleeping impairments but also psychotic like symptoms (Iyer et al. 2008b). High levels of negative symptoms that are associated with "at risk" states for psychosis, often indicate long periods of isolation and poor functioning (Yung et al. 2003). It is further recognized that a large portion of FEP patients may originate from backgrounds of compounding adversity (Matheson et al. 2013). Co-morbid mental health issues (Sim et al. 2006; Pope, Joober, and Malla 2013), including drug misuse (Archie et al. 2007), represents a further challenge.

In a study of subjective experiences of FEP, well over three quarters indicated they felt traumatised by their experience (Tarrier et al. 2007). There is evidence that following a FEP, some may be at a higher risk for post traumatic stress (Tarrier et al. 2007; McGORRY et al. 1991) and suicide (Birchwood et al. 2000). Feelings of anger and depression as well as increased hesitancy in maintaining and initiating social connections is a common reaction to a FEP (Birchwood 2003), particularly given the social stigma of mental disorders (Birchwood et al. 2007). While there is emerging evidence that a FEP may be an opportunity for growth and meaning (Jordan, Malla, and Iyer 2016), it is also widely agreed that those with a FEP constitute a particularly vulnerable population in need of care.

4.3 Conceptualizing the "critical period" and relevance to negative symptom outcomes in FEP

The critical period hypothesis (Birchwood, Todd, and Jackson 1998) posits that post FEP, there is a window of approximately 5 years during which illness trajectories may be most malleable to intervention and to better long-term outcomes. The origin of the concept of a critical period is largely accredited to the field of linguistics (Lenneberg 1967) but has been used widely in understanding brain development. In FEP, evidence to support the need for earlier intervention comes from several sources. Reports from 2 meta-analyses suggest that delay to treatment or DUP is associated with higher rates of relapse, greater symptomology, and worse functioning (Perkins et al. 2005; Marshall et al. 2005). That delay to treatment imparts greater treatment resistance (Wiersma et al. 1998), suggests a symptomatic plateau in FEP, estimated to be around 2 years (Birchwood and Fiorillo 2000). Indeed, there is large cross-cultural evidence that the pattern of positive as well as negative symptomology over the first 2 years of illness onset predicts clinical presentation and functioning 15 years later (Harrison et al. 2001; Harrison et al. 1996), with family involvement and the quality of health care as significant moderators (Harrison et al. 2001).

4.4 Evidence for a model of Specialized Early Intervention

Evidence of the role that comprehensive and high quality treatment provided early in the course of illness plays in determining long-term outcomes in psychotic disorders has spurred the

implementation of EI programs world-wide. EI is designed to provide phase specific intervention including low dose second-generation antipsychotics (SGA), evidence based psychosocial interventions (cognitive behavioural therapy, family intervention etc.) and assertive case management, modified to suit this phase of illness and developmental stage of young service users, with a low patient to case manager (1:20) ratio (Malla et al. 2003). EI services attempt to reduce delay in treatment, or DUP, by simplifying pathways to care, while others also engage in early case identification within the community (Larsen et al. 2001). Case managers within the program strive to form a strong working alliance and engage with patients in decision making, supporting them with a wide range of psychosocial and psychological interventions including individual and family psychoeducation and counseling, cognitive behavioural therapy (CBT), and vocational assistance. Evidence from the meta-analysis and systematic review presented confirms that it is unlikely that one aspect of the program may be responsible for the magnitude of benefit that FEP patients experience (Lutgens, Gariepy, and Malla 2017). Instead, it is likely that the multi-targeted approach with a strong case-manager -patient relationship at its base is needed to facilitate such extensive and wide reaching improvements. As EI programs are designed specifically to target the unique needs of a younger population, they also include family support. EI represent a paradigm shift away from treating symptoms as they become critical and instead aims towards prevention, early detection, and early intervention (Malla, Norman, and Joober 2005; Malla et al. 2016). While the critical period is suggestive of an optimal intervention period of 5 years (Birchwood, Todd, and Jackson 1998) most programs were designed only to cover the first 2 years suggested by cross-cultural outcome studies (Nolin et al. 2016; Grawe et al. 2006; Petersen et al. 2005; Craig et al. 2004).

There is ample evidence from both controlled and uncontrolled studies to support effectiveness of EI services on a wide range of outcomes (Nordentoft et al. 2014; Marshall and Rathbone 2011; Harvey, Lepage, and Malla 2007), including on rates of negative symptoms (Srihari et al. 2015; Harvey, Lepage, and Malla 2007). The most influential RCT from Denmark (OPUS) randomized 547 FEP patients into either 2 years of EI with a clinician caseload of 1:10, or treatment as usual in the community (Thorup et al. 2005). Those in EI demonstrated significantly lowered SANS negative symptoms at 2 years than those in regular care (95% CI: - 0.67 to -0.23) (Thorup et al. 2005). Two other studies from the same period, one with 144 FEP patients over 18 months (Garety et al. 2006) and another with 50 FEP patients over 2 years (Grawe et al. 2006) similarly reported significant negative symptom improvements in FEP. A single study (COAST), found no difference on negative symptom outcomes between 32 patients randomized to EI and 27 to TAU (Kuipers et al. 2004). However, this study was conducted over only 9 months and FEP was defined broadly as a first experience of psychotic symptoms within 5 years or less since study entry, with an upper age limit of 65 (Kuipers et al. 2004).

More recently, a study conducted in the US, Kane and colleagues (RAISE) randomized 34 community mental health clinics within 21 states to provide either SEI or TAU (Kane et al. 2015). In total, 404 FEP patients were randomized with 181 in TAU and 223 in EI, delivered without intensive case management. Although PANSS Negative subscale scores were not significantly different, those that received EI reported significantly better scores on QofL measures of "interpersonal relations", "intrapsychic foundations" and engagement with "common objects and activities" that correlate with negative symptom improvement. As well, a greater proportion of RAISE patients were either working or going to school at any time during each month than those in regular care (Kane et al. 2015). In another recent American trial,

Srihari and colleagues (2015) also found no difference in negative symptoms for 120 patients randomized to EI rather than regular care, although again, a significantly better vocational and educational score at treatment end was recorded (Srihari et al. 2015). Considering this study alongside that conducted by Kuipers et al., 2003, suggests that treatment of FEP, where FEP is more broadly defined as having had a first psychotic episode within 5 years (Kuipers et al. 2004), is likely to be associated with less negative symptom improvement. In sum, when a specialized model of EI is applied early, with a narrow definition of FEP and when considering also negative symptom correlates, EI is consistently successful compared to TAU in targeting and ameliorating negative symptoms.

4.5 Optimal duration of EI for negative symptom improvement?

Despite the benefits of EI on negative symptoms at 1.5-2 year treatment end, a 5 year follow-up found that there were few differences in outcomes, including in negative symptoms between those that had received EI or regular care, once both had received 3-years of regular care (Bertelsen et al. 2008). This finding has been widely interpreted to suggest that negative symptom improvements are not sustained over time, post EI end (Bertelsen et al. 2008). In response to this study, the Prevention and Early Intervention program in London Ontario, Canada offered all FEP patients that had received the standard 2 years of SEI, and additional 3 years of a stepped down model of EI for the entire 5 year critical period (Norman et al. 2011). Although this was a naturalistic study, findings from this trial were positive and showed that FEP patients at 5 year follow up had higher rates of remission, better functioning and in particular, less negative symptoms compared to OPUS patients at 5 years (Norman et al. 2011). The success of extended treatment within this study provided the rationale for a randomized controlled trial

(RCT) at the prevention and early intervention program in Montreal (PEPP-Montreal), Quebec to investigate the effect of extending EI for the full 5 year critical period.

The protocol that follows (Chapter 4) presents the framework for the RCT conducted between and 2008 and 2016. Negative symptom outcomes presented Chapter 5, and upon which this thesis is based, are derived from the RCT trial, but also on data from the first 2 years of EI, prior to randomization. Chapter 6 provides a summary of all findings and a reviews of its significance to our understanding of the treatment of negative symptoms in FEP.

Chapter 5: 'A five-year randomized parallel and blinded clinical trial of an extended specialized early intervention vs. regular care in the early phase of psychotic disorders: study protocol'

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STUDY PROTOCOL Open Access

A five-year randomized parallel and blinded clinical trial of an extended specialized early intervention vs. regular care in the early phase of psychotic disorders: study protocol

Danyael Lutgens[1], Srividya Iyer[2], Ridha Joober[3], Thomas G Brown[4], Ross Norman[5], Eric Latimer[6], Norbert Schmitz[7], Amal Abdel Baki[8], Sherezad Abadi[9] and Ashok Malla[10*]

Abstract

Background: Specialized Early Intervention services (SEI) for first episode psychosis are shown to be effective for the treatment of positive and negative symptoms, medication adherence, rates of relapse, substance abuse disorders, functional outcome and quality of life at two-year treatment follow up. However, it is also reported that these benefits are not maintained when SEI is not sustained. The objective of this trial is to test the efficacy of a 3-year extension of a SEI service (following 2 years of SEI prior to randomization) for the maintenance and consolidation of therapeutic gains as compared to regular care in the community.

Methods: Following an initial 2 years of SEI, patients are randomized to receive either 3-years of continued SEI or regular care. SEI provided at three sites within the McGill network of SEI services, using a model of treatment comprised of: modified assertive case management; psycho education for families; multiple family intervention; cognitive behavioural therapy; and substance abuse treatment and monitoring. Blinded research assistants conduct ongoing evaluation of the outcome variables every three months. The primary outcome measure is remission status measured both as the proportion of patients in complete remission and the mean length of remission achieved following randomization during the additional three years of follow up. Based on preliminary data, it is determined that a total of 212 patients are needed to achieve adequate statistical power. Intent to treat with the last observation carried forward will be the primary method of statistical analysis.

Discussion: The "critical period" hypothesis posits that there is a five year window during which the effects of the nascent psychotic illness can be countered and the impact of the disorder on symptomatic and functional outcomes can be offset through active and sustained treatment. Providing SEI throughout this critical period may solidify the benefits of treatment such that gains may be more sustainable over time as compared to intervention delivered for a shorter period. Findings from this study will have implications for service provision in first episode psychosis.

Trial registration: ISRCTN11889976

Keywords: Specialized early intervention, First episode psychosis, Treatment, Critical period, Remission, Case management, Randomized controlled trial

* Correspondence: ashok.malla@mcgill.ca
[10]Department of Psychiatry, McGill University; Director, Prevention and Early Intervention Program for the Psychoses, Douglas Mental Health University Institute, Montreal, Quebec, Canada
Full list of author information is available at the end of the article

Background

Psychotic disorders including schizophrenia spectrum and affective psychosis are considered among the most severe mental disorders [1], resulting in personal and family suffering [2,3] and associated with poor long term outcomes, particularly if not adequately treated [4-6]. The first episode of psychosis (FEP) typically occurs between adolescence and early adulthood [7] and interferes with educational and employment attainment as well as social transitions [8]. The life time prevalence of all psychotic disorders, that include the presence of at least one positive symptom, is up to 3.4% in the general population [9]. In Canada alone, the overall economic cost to society that includes loss of productivity as a result of psychosis is estimated at over six billion dollars per year [10].

While most patients will respond positively to initial treatment [11], the long-term prognosis is varied [12]. Only up to one quarter of all psychosis patients are likely to achieve complete remission, depending on the criteria and length of follow up applied [12,13]. Given such likely negative outcomes, emphasis has been placed on the earliest phase of psychosis, considered a "critical period" of five years [14] when patients' psychosocial health may otherwise be most likely to decline [15] unless long term health trajectories are re-established [16]. Specialized Early Intervention (SEI) programs were first initiated in the 1990s as a response to mounting evidence of the importance of prevention, early detection and appropriately targeted and timely treatment during this critical period [17].

In comparison to regular care where the majority of patients (80%) fail to sustain remission within the first five years [18,19], FEP patients treated in an SEI model, show higher rates of remission, lower rates of residual positive and negative symptoms, lowered rates of relapse, less substance abuse and better overall functioning at one and at two years [11,20-24]. Indeed, the benefits of SEI service as compared to treatment as usual over the short term have been verified by three randomized controlled trials [25-28] as well as uncontrolled studies (for a meta-analytic review see Harvey et al., 2007 [29]). Despite such encouraging outcomes, a five year uncontrolled study of FEP patients treated for 12 months in an SEI service and then transferred into regular care showed a loss of the beneficial effects achieved earlier in treatment [30]. Critically, in a five year follow up study (OPUS Trial) of a large sample of FEP patients, who had received two years of SEI service before being transferred to regular care, the therapeutic gains achieved at two years were not maintained over the following three years [31].

This loss of advantage seen over the subsequent three years during which SEI services were no longer available may have been prevented if the SEI service were continued throughout the critical five-year period in FEP. In a recent study conducted in Canada, a reduced level of SEI service was offered to all patients for three years beyond the standard first two years of SEI treatment [32]. Although there was no comparison group and the intensity of SEI was lowered, patient outcome data after five years (two years of SEI followed by three years of stepped down SEI) when compared to the five-year outcome data of OPUS patients who had only received two years of SEI treatment were significantly better (rates of remission and hospitalization) [32].

Based on the evidence reviewed above, the current study is being conducted to address this question of optimum treatment length using a randomized controlled (RCT) design at the Prevention and Early Intervention Program for Psychosis (PEPP-Montreal). In this RCT we evaluate the effect of three years of extension of full SEI services following two years of SEI, compared to three years of regular care following the initial two years of SEI service.

The primary hypothesis guiding this RCT is that individuals in the experimental group (extended SEI) will show higher rates and longer periods of remission (both positive and negative symptoms) than the control group over the extension period of three years. The *secondary hypotheses* are that: a) the difference in remission rates are mediated by the level of medication adherence in the two groups; b) as the experimental group is expected to have higher levels of working alliance with their treatment providers than the control group, we hypothesize that the difference in the level of medication adherence between the two groups and retention in treatment is predicted by working alliance; c) that the experimental group will have better clinical outcomes (lower relapse rates and levels of symptoms), functional outcomes (social/occupational functioning), and quality of life than the control group. The economic consequences of extending SEI past the standard current 2 years is also being investigated, within the RCT design, taking into consideration both direct and indirect costs.

Methods

Design

This trial is a randomized controlled trial comparing extended SEI for FEP (five years total) with treatment as usual for FEP (two years of SEI followed by three years of regular care). Prior to randomization, all patients received their treatment from the McGill University network of hospitals that offer SEI service according to a common model of care within a defined catchment area in the city of Montreal.

Inclusion criteria

Our aim is to use inclusion criteria that are as non discriminatory as possible in order to ensure the ecological validity of this trial and to reflect the kinds of diverse patients seen in FEP clinical settings. Although the SEI services treat patients between 14 and 35 years old, for the purpose of the study, patients aged 18–35, with a DSM-IV diagnosis of a psychotic disorder (schizophrenia spectrum psychoses and affective psychosis), who have completed two years of SEI treatment and follow-up within the McGill network of SEI services, an IQ greater than 70, the ability to communicate in either French or English, and the ability to provide informed consent, are eligible for participation. Patients are re- cruited regardless of their remission status at the end of two years of SEI treatment, consistent with what may be seen in regular clinical practice. Ethics approval for this RCT was granted by McGill University's Faculty of Medicine Institutional Review Board (Assurance number: FWA 00004545) and from the Douglas Hospital Research Ethics Board.

Exclusion criteria

Patients who are not able to provide informed consent (as determined by an inability to provide a brief sum- mary of the treatment protocol following presentation of the consent form); those with an inability to communi- cate in either English or French; and those with an I.Q. below 70 are ineligible for participation. Co-morbid sub- stance abuse and dependence is not an exclusion criteria.

Randomization

Randomization is stratified according to sex and substance abuse to ensure that these two factors, know to influence outcome, are balanced between groups. Once participants have signed informed consent to be randomized, their initials and ID # are given to an on site statistician who is not connected with the service. Randomization to one of the two treatment conditions is conducted using a computerized urn randomization protocol [33]. Post-randomization, patients are asked which condition they would have preferred to be randomized to and if they are satisfied with the allocation they were assigned. Results of the randomization are communicated to the treatment team such that appro- priate transfer decisions may be made, in the case that a patient is randomized to regular care. This data will be used as a covariate in case that treatment preference biases outcomes (Figure 1).

Recruitment

Patients who have received ongoing modified case management for the entire two-year period are screened for their participation. Patients that meet the inclusion cri- teria are approached for their participation between months 21 and 24 of SEI from one of the three McGill network SEI sites. The principal site of recruitment is the Prevention and Early Intervention Program for Psychosis (PEPP-Montreal), established in 2003 and the largest of the three sites; FEP Program at the Jewish General Hospital (established in 2007) and the PEPP at the McGill University Health Centre (established in 2009).

Participants

Blinding

Neither the participants nor case managers and other clinicians can be blinded to the assignment of the treatment condition. However, trained research staff, not involved in the patients' care and blinded to the treatment condition, conduct all assessments outside any of the patient treatment facilities. Baseline assessments are conducted as soon as possible, within the first 3-6weeks of randomization, in order to avoid revealing group assignment. This is done to prevent any possibility of bias in self-reports that could influence the comparability be- tween groups. In cases where the blind is broken, add- itional analyses, excluding the unblinded cases, will be conducted to test for any effect of unblinding.

Interventions

The experimental intervention

Patients randomized to three years of extended SEI service continue to have access to the entire package of SEI services for an additional three years, following the initial two years of SEI. The following services, offered at the main PEPP site, constitute the experimental intervention:

a. *Modified assertive case management* will continue to be one of the core treatment services provided. The case manager, with professional backgrounds primarily in social work or nursing, who has been involved in the patient's care in the first two years, continues to provide the same service. This includes supporting the patient towards the attainment of appropriate treatment goals with a moderate case manager to patient ratio (20:1). Goals of treatment typically emphasize adherence to antipsychotic medication, reintegration into employment and/or educational activities, improving patients' understanding about their illness, reducing dependence on hospital services, providing crisis intervention, promoting independence, monitoring early signs of relapse and reducing the risk of being engulfed by the illness. A personalized profile of the patients' early warning signs [34,35] is created jointly in collaboration with the patient and used as a tool

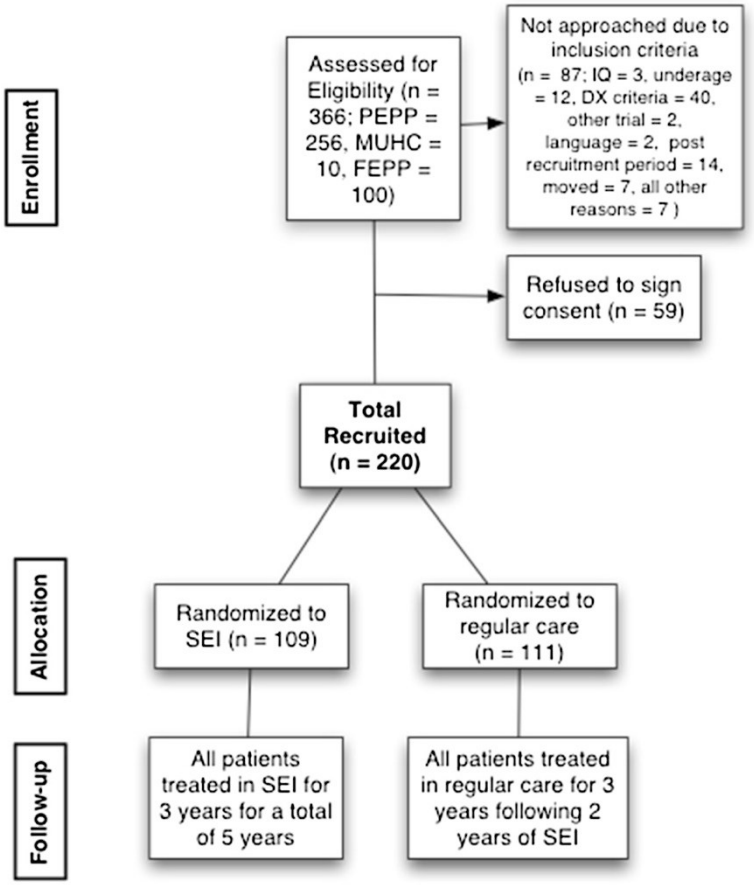

Figure 1 Diagram of study participants in PEPP trial of extended SEI.

for the patient and the case manager to monitor any symptoms that might signal future relapse. Case management is provided as per the patients' needs, using a guideline of a minimum of two contacts per month.

b. *Multiple Family Intervention* is offered to the patient's family as booster sessions of structured family education intervention and multiple family group intervention [36] similar to what is offered during the first two years.
b. *Psychoeducation for families* is offered once a year and as booster sessions to the patient's family. Workshops are designed as three two-hour sessions where families can ask questions and learn about psychosis, treatment and support.
c. *Cognitive behaviour therapy* (*CBT*), known to be highly effective for those with psychosis [37,38], is offered in the case of a major depressive episode, anxiety disorder or residual psychotic and/or negative symptoms.
d *Substance abuse education and monitoring* for problems associated with substance abuse is offered to patients who, at initial presentation had a co-morbid diagnosis of substance abuse or developed substance abuse during the first two years of treatment. Therapists have received training to provide a brief (one-two sessions of 40–60 minutes each) intervention based on Motivational Interviewing [39]. The administration of the Timeline Follow-Back procedure followed by feedback [40] is used to help patients track their own alcohol and drug consumption. Patients are referred to appropriate rehabilitation if needed.

The control intervention

Patients randomized to the control condition receive treatment as usual in general medical or regular psychiatric services that are available for free to all Quebec patients. Primary regular care in Quebec is predominantly offered through local health and community services centres (CLSCs) that provide health and social services to their catchment area. Care by a family physician in the community is provided in a variety of settings, including at CLSCs and private clinics, and is of variable quality and intensity. Secondary (psychiatric) regular care, including hospital in- and out-patient services,

offer a range of psychosocial rehabilitation services, that are part of regular care available to all patients randomized to the control condition.

Assessments

Evaluations and assessments are carried out at entry and every three months thereafter for the entire follow up period, or until withdrawal from the study, for both treatment conditions (details of assessments are provided in Table 1). If a patient withdraws, they are asked to provide one last assessment. When no contact has been made for 3 consecutive assessment periods (for a total of 9 months) and attempts made for contact through phone calls, emails, and contact with care providers including family members, are not successful, the patient is considered to be withdrawn. Trained evaluators will conduct assessments largely through a semi structured interview format.

Data on the Duration of Untreated Psychosis (DUP) are available for all PEPP patients and is derived using the Circumstances of Onset and Relapse Schedule (CORS) [11], a structured interview instrument for use with patients and families that includes some sections from the Interview for the Retrospective Assessment of Onset of Schizophrenia (IRAOS) [54]. DUP data for all other patients is available through chart verification.

Outcomes

In light of more recent consensus criteria for remission that emphasizes the amelioration of positive as well as negative symptoms and a return to social and occupational functioning [55], a full range of complementary measures of clinical and functional outcome is being examined both separately and in context with each other.

Primary outcome

The primary outcome is complete remission measured as both the proportion of patients in remission, as well as the mean length of remission achieved following randomization during the additional three years of follow up. Complete remission is defined according to consensus criteria as a rating of mild or less on the following positive and negative symptom scale items (Positive domain: hallucinations, delusions, bizarre behaviour, positive formal thought disorder; Negative domain: affective flattening or blunting; alogia; avolition-apathy;

Table 1 Assessment instruments

Assessment	Instrument
Psychopathology	Scale for the Assessment of Positive Symptoms (SAPS) [41]*
	Scale for the Assessment Negative Symptoms (SANS) [42]*
	Positive and Negative Syndrome Scale (PANSS) [43]*
	Brief Psychiatric Rating Scale (BPRS) [44]*
Functioning	Global Assessment of Functioning Scale (GAF) [45]*
	Social and Occupational Functioning Scale (SOFAS) [46]**
	Productivity Interview Questionnaire (adapted from the Client Socio-Demographic and Service Receipt Inventory) [47]*
	Life Skills Profile [48]**
Medication and side effects	Patient Compliance Interview [49]*
	Medication Compliance: Pill Count Form [49,50]*
Substance use	Chemical Use/Abuse/Dependence-Scale (CUAD) [51]*
	Time Line Follow Back [40]*
Working alliance	Working Alliance Inventory (WAI) [52]**
Randomization preference	Self administered questionnaire***
Quality of life	Life Satisfaction and Psychological Well-being domains of the Wisconsin Quality of Life-Client version [53]**
Duration of untreated psychosis	Circumstances of Onset and Relapse Schedule (CORS) [11]***
Promorbid adjustment	Premorbid Adjustment Scale (PAS) [52]***
Service use including hospital admittance and total bed days	Self administered questionnaire with list of services received
	Regie de l'Assurance-maladie du Quebec (Quebec medical insurance; RAMQ)****
	Med-Echo (for hospitalizations)****

*Assessed at each evaluation (every 3 months).
**Assessed at every second evaluation (every 6 months).
***Assessed once at baseline.
****Assessed post study completion.

anhedonia-asociality) for a period of six months [55]. Complete remission is chosen as the primary outcome measure as per findings that remission across both symptom domains is a better predictor of functional outcome than remission of positive symptoms alone [56,57]. Remission is measured at each assessment covering the three months prior using the Scale for Assessment of Positive Symptoms [41] and the Scale for the Assess- ment of Negative Symptoms [42]. The SANS domain of Attention is not included in SANS ratings as these items have not been shown to correlate to the domain of negative symptoms [58].

Secondary outcomes

a) *Clinical outcome*: (i) Relapse (defined as the reemergence of positive symptoms as measured by a global item on the SAPS of at least 3 in severity that leads to an increase or change in antipsychotic medication or to hospital admission) [59]; (ii) Level of positive and negative symptoms (SAPS [41] and SANS [42] ratings); (iii) Global Assessment of Functioning (GAF) [45]; (iv) Discontinuation of treatment as determined through a lack of service use.
b) *Functional outcome* (assessed on two functional dimensions): (i) role functioning (paid employment, school attendance, and/or meaningful housework) and through; (ii) social functioning (such as independence in community living) assessed using the Life Skills Profile [48] as well as the Social and Occupational Functioning Scale (SOFAS) [46] as a global measure of functioning.
c) *Quality of Life* (*QOL*): Subjective reporting of QOL is assessed at study entry and subsequently at every six months using the Life Satisfaction and Psychological Well-being domains of the Wisconsin Quality of Life-Client version [53].

Mediating variables

a) *Adherence to medication* is assessed through patient and family reports (when available), and pill counts are conducted by the evaluator. Ratings are made on a five point scale ranging from 0 = not taking medication when prescribed, to 5 = taking medication all of the time as prescribed.
b) *Working alliance* with respective service providers is measured with the Working Alliance Inventory-patient version, a self-report instrument [52]
c) *Premorbid adjustment* has been shown to be of importance to clinical outcome [11,18] and is assessed with the Premorbid Adjustment Scale [60] at time of entry into the trial in case that such data was not already collected as part of the initial protocol of entry into PEPP-Montreal.

Economic analysis

Administrative databases are utilized to assess costs associated medical services. The Regie de l'Assurance-maladie du Quebec (RAMQ) provides free public health and prescription drug insurance plans to all eligible Quebec residents. RAMQ databases are consulted for physician services (all patients) and filled prescriptions for patients with public coverage (approximately 90% of patients), and Med-Echo, for hospitalizations. Question- naires, administered at baseline and every three months following are utilized to record data on any other health care usage as well as for patient and family time involve- ment in receiving such treatment. We request consent to access this database as part of the initial informed consent. This information is used to track overall soci- etal and economic costs associated with patient treat- ment in both the experimental and control groups.

Training and inter-rater reliability

All service care providers and assessors acquire intensive onsite training in their field and are supervised by the principal investigator (A.M), co-PI (R.J) and the PEPP research coordinator (S.A). Assessors have achieved high inter rater reliability (range 0.75-0.92) and are able to consult with the project coordinator should any ques- tions arise.

Power and sample size

Power Analysis for sample size calculation is based on the proportion of SEI patients that were in remission of positive symptoms in the last two years of the OPUS trial (41.8%) [31] and the proportion of SEI patients that were in remission in the last two years of the uncon- trolled outcome study conducted at PEPP–London (69%) [32]. Assuming conservatively a 5% greater pro- portion of patients in remission for the control condition than in the OPUS trial and a 5% smaller proportion for the experimental condition than in the PEPP-London study, it is estimated that a sample size of 82 in each group (total of 164) will achieve 80% power to detect a difference between groups. Given the rates of attrition between the beginning of the third and the end of the fifth years from the OPUS extension trial that were 18%
[31] and from the PEPP-London study that were 12% [32], we expect rates of 25% and <20% over the same period from the control and experimental conditions respectively. Recruitment of participants are adjusted from n =164 to n = 212 to account for possible dropouts.

Participant withdrawal

For the purpose of this trial, dropouts are considered those with three assessments in a row that are missing. To reduce attrition, our study coordinator contacts anyone who has missed two assessments in a row, prior to their next scheduled evaluation. When a drop- out has occurred, an effort is made to ascertain the reason for the dropout and to conduct a final assess- ment for the primary outcome (remission status). If a patient drops out of treatment but continues to con- sent to using their data, medical files for their case are located to obtain information on many of the outcome measures.

Statistical analyses

Data analysis is based on the intent to treat principle. All patient evaluations will be included in the analysis. To assess homogeneity at baseline, relevant demographic data will be presented.

For the primary outcome measures, the proportion of patients in remission in the experimental and con- trol groups will be compared using a Pearson chi- square statistic and the mean length of remission with a t-test or Wilcoxon test for independent samples, based on the distribution of the independent variable. Logistic regression analyses and multiple regression analyses will also be performed with all covariates and mediators.

For the secondary outcome measures including relapse (relapse vs. no relapse), dichotomous outcomes will be analyzed using logistic regression with covariates. Time to Event (relapse) will be measured using a Kaplan- Meier methods and Cox regression to analyze intervals of time from randomization to relapse. Continuous out- comes that include clinical outcomes will be assessed using regression models with covariates and finally lon- gitudinal data with repeated measurements will be ana- lyzed using repeated measures of analysis of variance.

Missing data will be assessed to determine if they are random or informative. Should missing data be non ig- norable, then selection models and pattern-mixture models will be used to evaluate the robustness of the primary analyses.

Ethical considerations

All patients randomized to either continued SEI or to regular care following two years of SEI are offered treat- ment according to best practice. Participants are in- formed about the trial and about the voluntary nature of their participation with both written and verbal commu- nications. Participants are only randomized following the provision of informed consent.

Trial status

Currently all participants (n = 220) have been recruited and are randomized with n = 109 in the experimental group and n = 111 in the control condition (extended SEI vs. regular care). Participants are being followed with the last patient assessments scheduled for 2015.

Discussion

This study is based on previous data that suggests that the benefits of SEI services in FEP at two years are lost at five-year follow up if patients return to regular care [31]. Given the severity of psychosis and the individual and societal costs associated with this disorder, there is a need for research that can better guide best practices. That FEP patients are young and potentially still malle- able to treatment, suggests the importance of positively influencing long-term trajectories of outcome. To our knowledge, this is the first RCT trial of its kind in North America, and one of only two such trials anywhere (OPUS-II) [61], being carried out currently to assess the impact of extended SEI for a total of five years in FEP. Several strengths of this study include the number of participants recruited as well as the computerized randomization procedure that ensures chance allocation to group. That we have included FEP patients with co- morbid disorders, including comorbid substance use, and that patients in our control condition are likely to be filtered through a wide range of 1st, 2nd, and 3rd line services available, gives critical construct validity to our study. Given that the majority of service is provided out of a single site (PEPP-Montreal) with two satellite clinics that are closely aligned and that follow the same treat- ment system, homogeneity of service infrastructure and fidelity to the same SEI model of care is ensured. As well, we are measuring a host of critical variables that may give meaning to the context of remission. Variables including social and occupational functioning and nega- tive symptoms at baseline have been shown to impact long-term trajectories in FEP [12,13]. Measures of quality of life bring into focus the personal perspectives of this disorder while concurrent measures of all associated economic costs will highlight societal burden. This trial is registered http://www.isrctn.com/ (ISRCTN11889976), which helps to ensure complete reporting.

A limitation of any service based trial is that we are unable to blind participants or service providers to treat- ment allocation. While participants may not receive their preferred allocation in either condition, this possi- bility is discussed beforehand. That assessors are inde- pendent of treatment providers and conduct their evaluations blind to the treatment allocation outside of the patients' treatment location will reduce chances of unblinding the treatment assignment and ensure the in- tegrity of symptom and functional assessments.

Potential impact of the results

Despite the growth of SEI services across the world, the optimum length of SEI services in FEPP has not been ascertained and remains an important issue for treatment providers, service users, and policy makers. Results of this RCT are likely to have major impact on treatment of FEP and the recommendation of an optimal duration of SEI services. Should an extension of SEI serve to improve outcomes for patients with a FEP, this will be a major benefit to individuals, families and to society.

Abbreviations

RCT: Randomized controlled trial; SEI: Specialized early intervention; FEP: First episode psychosis; PEPP: Prevention and early intervention program for psychosis; CLSCs: Community services centres; RAMQ: Regie de'lAssurance-maladie du Quebec; MUHC: McGill University Health Centre.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DL: As part of her PhD thesis, conducted literature reviews and drafted first and subsequent drafts of the manuscript under supervision of AM SI: Original contribution towards study design and implementation. RJ: Co-Principal Investigator (same as above). TGB: Original contribution towards the role of substance abuse and its treatment; to the process of randomization and to evaluation of substance abuse. RN: Fundamental contributions towards the design of the study, based partly on a study he led evaluating the effect of stepped down Early Intervention Services over an extended period. EL: Original contribution towards designing the evaluation of economic impacts of the experimental and control interventions. NS: Original contribution towards the statistical analysis plan of the study and for taking responsibility for randomization. AAB: Contribution towards the conceptual framework of the study proposal. SA: Contribution to organizing and coordinating the trial at all sites. AM: Created the original idea and wrote the original draft of the study proposal for funding and the study protocol; supervised all aspects of setting up the trial. All authors have independently read and have approved of the final manuscript for submission.

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Author details

[1]Department of Psychiatry, McGill University; Prevention and Early Intervention Program for the Psychoses, Douglas Mental Health University Institute, Montreal, Quebec, Canada. [2]Department of Psychiatry, McGill University; Program Coordinator, Prevention and Early Intervention Program for the Psychoses, Douglas Mental Health University Institute, Montreal, Quebec, Canada. [3]Department of Psychiatry, McGill University; Assistant Director, Prevention and Early Intervention Program for the Psychoses, Douglas Mental Health University Institute, Montreal, Quebec, Canada. [4]Department of Psychiatry, McGill University; Douglas Hospital Research Centre, Montreal, Quebec, Canada. [5]Department of Epidemiology and Biostatistics, Western University; Prevention and Early Intervention Program for Psychoses (PEPP), London Health Sciences Centre, South Street Hospital, London, Ontario, Canada. [6]Social and Transcultural Division, Department of Psychiatry, McGill, University; Douglas Hospital Research Centre, Montreal, Quebec, Canada. [7]Department of Psychiatry & Department of Epidemiology and Biostatistics, McGill, University; Douglas Hospital Research Centre, Montreal, Quebec, Canada. [8]Department of Psychiatry, Université de Montréal, Research Centre CHUM, Montréal, QC, Canada. [9]Coordinator, Prevention and Early Intervention Program for the Psychoses, Douglas Mental Health University Institute, Montreal, Quebec, Canada. [10]Department of Psychiatry, McGill University; Director, Prevention and Early Intervention Program for the Psychoses, Douglas Mental Health University Institute, Montreal, Quebec, Canada.

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Progress of Negative Symptoms Over the Initial Five Years of a First Episode of Psychosis

Danyael Lutgens[1]; Ridha Joober[2;] Srividya Iyer[3]; Martin Lapage[4]; Ross Norman[5]; Norbert Schmitz[6]; Sally Mustafa[7]; Sherezad Abadi[8]; Ashok Malla[*]

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[1, 2, 3, 6,7,8] Department of Psychiatry, McGill University, Douglas Mental Health University Institute; Prevention and Early Intervention Program for Psychosis (PEPP-Montreal), Montreal, QC, Canada

[5]Department of Psychiatry, Western University; Prevention and Early Intervention Program for Psychosis (PEPP – London) London, Ontario, Canada

[4, 6,] McGill University, Douglas Hospital Research Centre, Montreal, QC, Canada

*Address for correspondence:

Prof. Ashok Malla,

McGill University,

ACCESS Open Minds,

Douglas Mental Health University Institute,

6625 Boulevard Lasalle,

Montreal, QC H4H 1R3

Ph: 514-761-6131 ext. 6209; Fax: 514 888-4458

ashok.malla@mcgill.ca

Abstract

Background: Specialized early intervention (EI) services for 2-years following a first episode of psychosis FEP are effective at reducing negative symptoms, although its trajectory warrants systematic assessment. Further, findings are equivocal as to whether extended gains are made post 2 years of EI and whether there is additional benefit of extending EI for an additional 3 years.

Methods: Data was obtained from a randomized controlled trial of a three-year extension of EI service vs transfer to regular care following two years of EI service. Analysis of 178 FEP patients was conducted over the initial two years of treatment in an EI service and, after patients were randomized (1 :1) beginning at the end of the second year of EI treatment, to either EI or regular care for an additional 3 years.

Results: There were significant improvements in total negative symptoms over the first 2-years of EI $F(4.612, 797.905) = 25.263$, $p < 0.001$ and in domains of 'expressivity' and 'motivation'. In the following 3 years, there were further significant improvements in negative symptoms $F(4.318, 759.908) = 4.182$, $p = 0.002$ with equality between groups $F(4.318, 759.908) = 1.073$, $p = 0.371$. Changes in negative symptoms over the extension trial were driven by expressivity $F(4.01, 705.96) = 7.37$, $p < 0.01$ but not motivation $F(5.527, 972.67) = 1.028$, $p = 4.03$.

Conclusion: Negative symptoms improve significantly over the first 2-years of EI. Subsequent amelioration was largely the result of expressivity. Motivation deficits remained stable. Extended EI offered no advantage over regular care post-randomization.

Key words: negative symptoms, specialized early intervention, extended specialized early intervention, first episode psychosis, expressivity, motivation.

Introduction

Negative symptoms (blunted affect, impoverished communication, lack of motivation, and social withdrawal), an important component of psychotic disorders, tend to emerge early in the course of illness [1]. They are significantly associated with poor quality of life [2] as well as social, educational, and occupational achievement [3]. Up to 30% of first episode psychosis (FEP) patients demonstrate moderate to severe negative symptoms that persist for at least 6-months [4, 5]. In a substantial proportion of patients, negative symptoms remain throughout the course of illness [3]. Antipsychotic medications, effective in treating positive symptoms, have limited impact on negative symptoms [6]. Meta-analyses of the effectiveness of psychological and psychosocial interventions, show only a modest to moderate effect [6,7].

For the first couple of years following the onset of psychosis, combined medical and multiple psychosocial interventions provided within specialized early intervention (EI) services produce a superior outcome compared to regular care [7-9]. While an earlier study reported that the initial improvement in negative symptoms achieved in an EI service was not maintained when patients were transferred to regular care [10], a Canadian study later reported that treatment in an EI service for 2-years followed by 3-years of lower intensity EI resulted in retention of earlier gains in negative symptoms [11]. Most recently, two randomized controlled trials (RCT) of extended EI (EEI) compared to regular care, following an initial 2-years of EI service, have been conducted. One study reported no benefit of a 3-year EEI, while the other reported a significant benefit of a one-year of EEI [12] that was not maintained post transfer into regular care, at 4-year follow-up [13]. While studies have examined negative symptoms from EI entry to 2-year EI follow-up, and later at 5 years, following either extended EI or regular care, this has not yielded a comprehensive examination into the trajectory of negative symptoms throughout this critical period of the first five years. Further, it is unclear whether symptoms improve further and/or differentially within extended EI compared to transfer to regular care for the final 3-years of a hypothesized five-year critical period in FEP, during which long-term outcome trajectories are most likely established [14, 15].

In the recently published report of an RCT of 3-years of extended early intervention (EEI) vs regular care following two years of EI service, on the primary outcome of length of total

(positive and negative) symptom remission as per consensus definition [16], patients in the extended EI had superior outcome compared to those transferred to regular care [17]. While meeting criteria for remission of negative symptoms requires an almost total absence of symptoms, it does not allow an examination of change in the level of symptoms over time. Further, we did not examine the initial progress of negative symptoms over the first two years and whether that progress is maintained or further improved in subsequent years differentially in an EEI service or regular care. The present report, therefore, is an analysis of planned secondary outcome measures [18] from the primary study [17]. It is restricted to patients who participated in the RCT and for whom data from regular assessments of negative symptoms throughout the initial-2 years of EI service were available.

Our objectives, therefore, were:

1. To examine the longitudinal course of negative symptoms over an initial period of 2 years in a large sample of previously largely untreated FEP patients treated in an EI service;
2. To determine if further gains in the level of negative symptoms can be achieved over the subsequent 3 years; and if so, whether such gains are greater in EEI compared to regular care.

Methods

Design

This study was conducted at the Prevention and Early Intervention Program for Psychosis (PEPP – Montréal). PEPP-Montréal provides assessment and treatment for all individuals presenting with a FEP in a catchment area of 300, 000 in South West Montreal, Quebec. Patients who meet the following criteria are admitted: age 14-35 years; a diagnosis of a first episode of non-affective or affective psychotic disorder; having received antipsychotic medication for no longer than 1 month; and an IQ above 70.

The study is of patients aged 16-30 who completed 2 years of treatment for a FEP at the PEPP-Montréal site and who then at the end of two years of EI service participated in an RCT comparing outcomes of either EEI or transfer to regular care for an additional 3 years. Hence,

this secondary report is based on negative symptom data for the same cohort of PEPP- Montréal patients over two phases:

In the *first phase,* we examined the trajectory of negative symptoms in FEP within the EI program from entry to treatment end (2 years). EI service is centered around assertive case management and provides low dose antipsychotic medication as well as psychological and psychosocial interventions aimed at recovery that includes personally set goals such as reintegration into employment and/or education, reducing hospitalization, and increasing independence. Other services include individually targeted Cognitive Behavioural Therapy (CBT) as well as family interventions (family psycho-education, multiple group family intervention and family support group) [19, 20].

In the *second phase*, we investigated whether any reduction in negative symptoms over the first 2 years was lost, maintained or enhanced over the subsequent 3 years and, if such benefit was greater in EEI than in regular care. At the end of the first phase (24 +- 3 months), patients were randomized to either continue in an EEI service or be transferred to regular care. Randomization was conducted using computerized urn randomization by a statistician not connected with the service. As sex and substance may influence outcomes, these factors were pre-stratified across conditions (see earlier publication[17]). The extension of EI continued to comprise assertive case management and multiple psychosocial interventions, described in detail in the primary report [17]. Regular care comprised of transfer either to primary care (family physician with or without additional support from other health and social service professionals) or to psychiatric clinics attached to the parent hospital.

Assessment

Negative symptoms, measured using the Scale for the Assessment of Negative Symptoms (SANS) [21], was the primary outcome of interest with total item scores from the following subscales: Affective Flattening or Blunting, Alogia, Avolition-Apathy, Anhedonia-Associality. Negative symptoms may not be a homogenous dimension and likely comprise 2 dimensions, motivation and expressivity [4, 22], although studied less in FEP. Both are associated with functional outcomes [2] but may follow distinct trajectories over time and be influenced by

different factors [23]. We, therefore, undertook an examination of change in these two dimensions in addition to total negative symptoms as a single entity. For this purpose, we first conducted a principal component factor analysis, with a varimax rotation, on all SANS items using the entire sample at baseline entry to EI. Factors with an Eigen value of 1.0 or greater were retained and items with a loading of greater than 0.5 were included in the particular factor. We forced a two-factor solution based on findings from previous studies, including those in FEP, suggesting a model of core negative symptoms contained within two dimensions [4, 22].

Symptom assessments were conducted through in-person interviews by trained research staff at entry (baseline) and months 1, 2, 6, 9, 12, 18, and 24 for phase I. Phase II assessments (post-randomization) were conducted at baseline (time of randomization) and then every 3 months over the 3 year post-randomization period. Each assessment covered symptoms for the prior 3-month period. For a proportion of patients (N = 53, 30%), the assessment conducted at month 24 (last assessment of year 2) overlapped with the date for the baseline randomization assessment and as such, was carried forward. Following randomization, all patients were assigned a new evaluator, trained within the framework of the RCT and blinded to group assignment. This same evaluator conducted the majority of assessments throughout the entire EI extension phase. Assessors achieved high inter rater reliability both throughout the initial 2-years of EI and post randomization, whenever additional assessors were utilized (range 0.75-0.92). For outcome on negative symptoms, a repeated measures ANOVA was conducted separately across phases I and II, first for all Negative Symptoms (Total) and then separately for each of the two dimensions identified through factor analysis.

Missing Observations and Data Imputation

Empty data points, fewer within phase I and more within phase II, were due to patients missing some assessments. When an assessment was missing and symptom data was available from files, assessments were retrospectively reconstructed. For the primary analyses, all patients were included if they had a baseline and at least one post baseline assessment at any time point. Missing data was imputed using the LOCF until the next available assessment data or to the end of the trial when there was no subsequent data. This is considered to provide a conservative estimate of change over time [24]. Sensitivity analyses were then conducted across both phases,

utilizing LOCF with trial completers only, such that those with more than 3 consecutively missing observations (a priori criterion for definition of drop out from the RCT) were excluded from the analysis.

Results

Demographic data

Demographic data for the cohort of 178 patients who entered the EI service (PEPP-Montreal) and who were subsequently randomized at 2 years (+- 3 months) to receive either EEI (n = 90) or treatment as usual (n = 88) is available in table 2. There were no significant differences on any measure at time of randomization.

Factor Analysis

A principal components analysis of total SANS items (excluding all attention items) conducted on the data at the time of entry to treatment revealed 2 factors. Factor 1 included all items on the affective flattening subscale (except inappropriate affect) as well as the poverty of speech and latency of response items on the alogia subscale. This factor likely reflects the dimension of 'expressivity' and explained 37.64% of variance in negative symptoms. Factor 2, that included all items on avolition and social anhedonia subscales (except sexual interest) typically identified as the dimension of 'motivation' explained an additional 10.42% of variance for 50% of the total variance explained (see Table 1). The same analysis at RCT baseline (phase II) revealed identical dimensions and similar loadings (except for the addition of sexual interest under factor 2) with a total of 49% of the variance explained.

Two-year outcomes

A repeated measures ANOVA with time (9 levels) as the Within Subjects Factor on 176 subjects revealed significant improvement over time in total negative symptoms with a Greenhouse Geisser correction $F(4.595, 799.577) = 25.246$, $p < 0.001$, partial $\omega^2 = .127$ (see figure 1). Post hoc tests reveal significant mounting improvements among all pairwise comparisons except for a period of stability across assessment months 9, 12 and 18 ($p > 0.05$). An analysis conducted separately for each dimension found Expressivity to have improved significantly over time using a Greenhouse Geisser correction $F(5.11,887.94) = 12.90$, $p < 0.01$, partial $\omega^2 = .625$ (see figure 2). There was also a significant improvement on the Motivation dimension using a Greenhouse

Geisser correction *F(5.21,912.21*) = 37.94, p = < 0.01 partial ω^2 = .178 (see figure 3). Post hoc tests show that the expressivity dimension did not continue to improve significantly between the 3rd and 18th month (p>0.05) while the motivation dimension did not show significant additional improvement between months 9 to 24 (p>0.05). Mean total negative symptom scores across each time point for the first 2 years of EI is available in the supplementary table.

Outcomes from years 3-5

A Mixed ANOVA with N = 175 revealed significant improvement in mean total negative symptoms over time for all patients in the test of Within Subjects Effect with a Greenhouse Geisser correction F(4.32, 759.908) = 4.182, p = 0.002, partial ω^2 = 0.023. There was no significant effect of group on total negative symptoms F(1, 176) = 0.11, p = 0.74, partial ω^2 = 0.001. The interaction effect of time (13 levels) and group (EI = 88, control = 90) was not significant F (4.318, 759.908) = 1.073, p =0.37, partial ω^2 = 0.006 (see figure 4), with no difference in improvement over time between the experimental and control group. Post hoc tests indicated that after the 6th assessment (month 15 post randomization), there were no significant improvements among all pairwise measures (p >0.05). Mean total negative symptom scores across each time point and for each condition of the RCT is available in the supplementary table 2.

In the test of Within Subjects Effect with a Greenhouse Geisser correction *F(4.01, 705.96*) = 7.37, p < 0.01, partial ω^2 = 0.045, the expressivity dimension was found to significantly improve over time, with no significant effect of group F(1, 175)= 0.021, p 0.88, partial ω^2 = 0.000 and no significant time X group interaction *F*(4.01, 705.96) = 1.01, p =0.40, partial ω^2 = 0.006 (see figure 5). Post hoc tests reveal that there were no significant changes in the expressivity dimension after the 12-month assessment (post-randomization). There was no significant effect of time on the motivation dimension as shown in in the test of Within Subjects Effect with a Greenhouse Geisser correction *F(5.527, 972.67*) = 1.028, p = .40, partial ω^2 = 0.006 and no significant group F(1, 176)=0.173, p = 0.678, partial ω^2 = 0.001, nor time X group interaction *F*(*5.527, 972.67*) = .837, p =0.53, partial ω^2 = 0.005 (see figure 6).

Total negative symptoms and change in expressivity and motivation over the entire 5-year period are shown in Figures 7, 8, and 9.

Missing observations and Sensitivity analyses

While the median of missed data at any given time point within the first 2-years of EI service was comparatively low: 14% (n = 24; range: 2% (n = 3; baseline) and 19% (n = 33; month 3), there was substantial missing data post randomization: 51% (n = 112; range: 21% (n = 46; baseline) and 64% (n = 141; month 36). Post Randomization, a total of n = 98 (mean per period = 7.5, 4.2%) assessments were reconstructed across all months for the 178 patients randomized. We restricted the next series of analyses (phase II) to subjects who had completed the entire 36-month of, post randomization research protocol. We found significant improvement in mean total negative symptoms over time for all patients in the test of Within Subjects Effects with a Geenhouse Geisser correction $F(4.723, 495.967) = 5.037$, $p<0.001$, partial $\omega^2 = .046$. There was no difference in outcome according to group randomization $F(4.723, 495.967) = .662$, $p =.643$, partial $\omega^2 = .006$. In the test of Within Subjects Effect with a Greenhouse Geisser correction, there was a significant improvement over time in the expressivity dimension with $F(4.34, 425.542) = 7.47$, $p < 0.00$, partial $\omega^2 = 0.071$ but no significant time X group interaction $F(4.34, 425.542) = .873$, $p =0.49$, partial $\omega^2 = 0.009$. There were no significant effect of time on the motivation dimension in the test of Within Subjects Effect with a Greenhouse Geisser correction $F(6.036, 633.77) = 1.726$, $p = .11$, partial $\omega^2 = 0.016$. There was also no significant time by group interaction $F(6.036, 633.77) = .837$, $p =0.44$, partial $\omega^2 = 0.009$.

Table 1. Demographic and clinical characteristics

	At baseline entry	At baseline randomization		
	Total (N=178)	Total (N=178)	Regular Care (N=88)	EEI (90)
Age at onset of first-episode psychosis (years, mean±SD)	22.4±4.4			
Marital status (single: N, %)	154 (86.5%)			
Education (high school or less, N, %)	57 (34.1%)			
Duration of untreated psychosis (weeks, mean±SD)	55.7±135.2 (median=13.28 weeks)			
Gender (male: N, %)	118 (66.3%)			
Primary diagnosis (schizophrenia spectrum, N, %)	114 (65.1%)	117 (65.7%)	61 (52.1%)	56 (47.9%)
Secondary diagnosis (substance abuse/dependence, N, %)	97 (54.5%)	97 (54.5%)	47 (48.5%)	50 (51.5%)
Antipsychotic at baseline (yes, N, %)	160 (92%)	137 (85.6%)	69 (42.5%)	68 (43.1%)
General Assessment of Functioning (mean±SD)	28.7±6.4 (N=174)	61.25±16.6 (N =134)	59.04±16.32	63.53±16.7
SAPS total score (mean±SD)	35.78±14.52 (N=175)	14.42±12.16	13.7±11.0	15.1±13.3
SANS total score (mean±SD)	25.77±13.65 (N=175)	14.42±12.16	15.10±13.26	13.73±10.96

EEI – extension of early intervention service, SAPS – Scale for the Assessment of Positive Symptoms, SANS – Scale for the Assessment of Negative Symptoms

Figure 1.

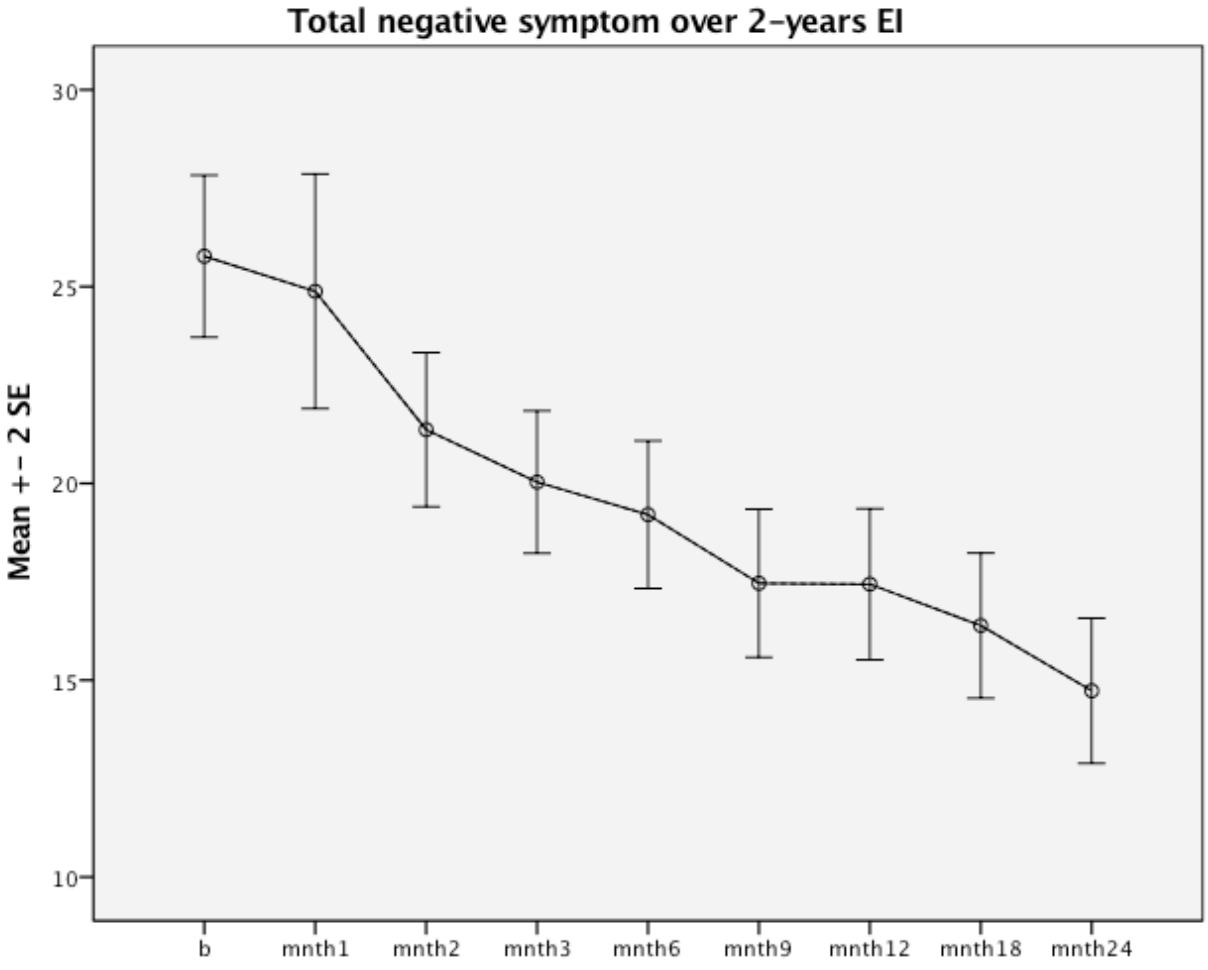

Total negative symptom over 2-years EI
Mean +- 2 SE
30
25
20
15
10
b
mnth1
mnth2
mnth3
mnth6
mnth9
mnth12
mnth18
mnth24

Figure 2

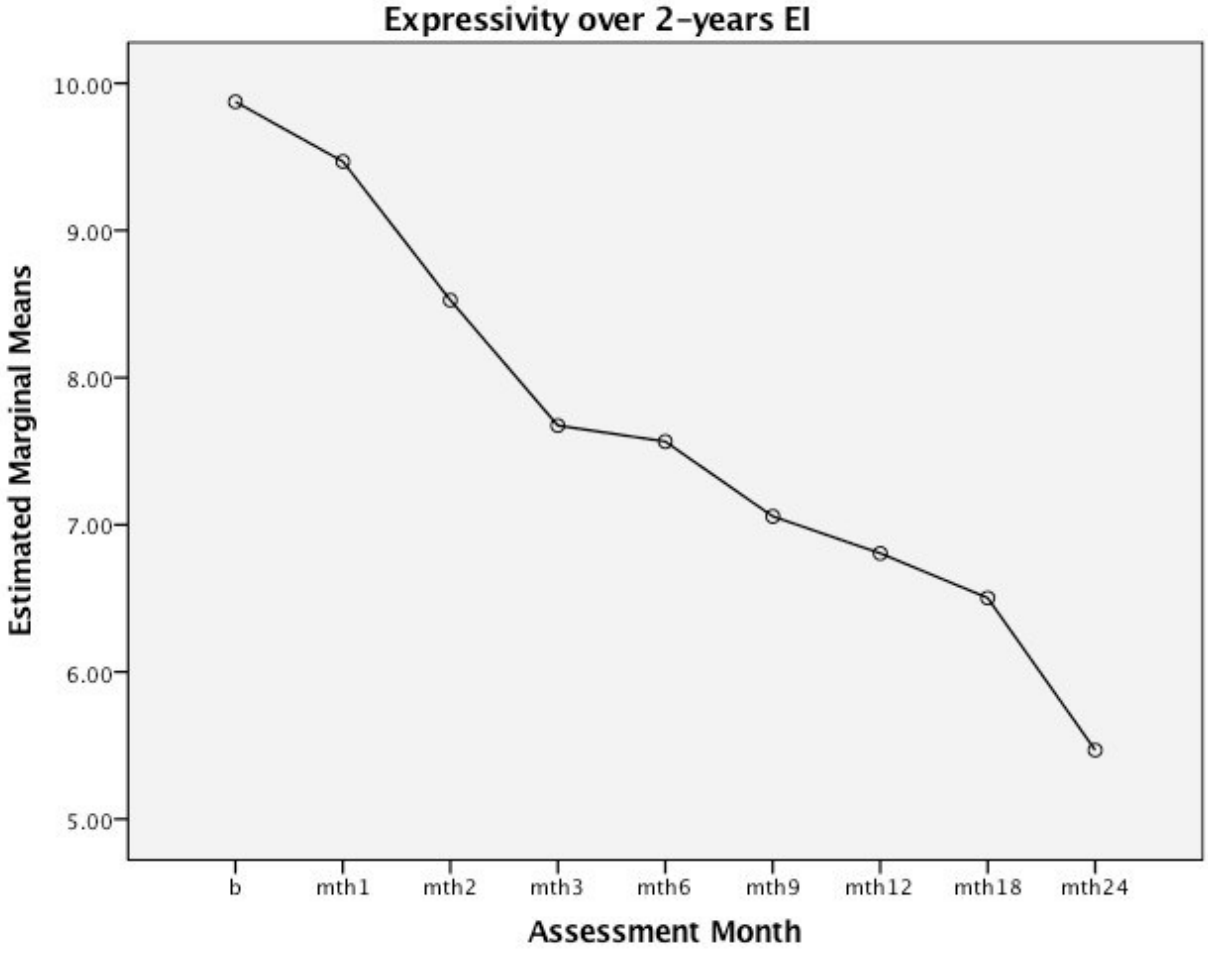

Expressivity over 2-years EI
Estimated Marginal Means
10.00
9.00
8.00
7.00
6.00
5.00
b
mth1
mth2
mth3
mth6
mth9
mth12
mth18
mth24
Assessment Month

Figure 3.

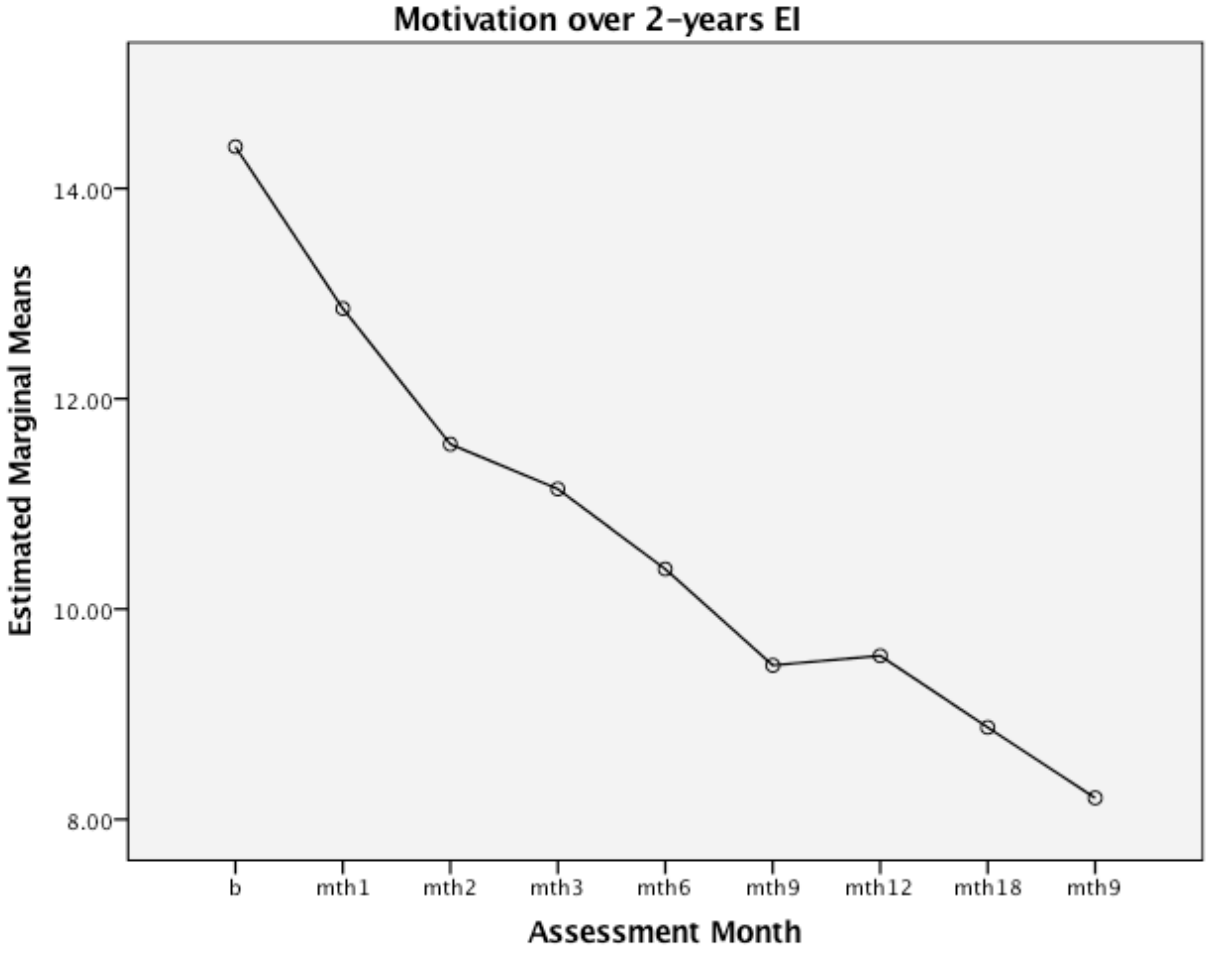

Motivation over 2-years EI
Estimated Marginal Means
14.00
12.00
10.00
8.00
b
mth1
mth2
mth3
mth6
mth9
mth12
mth18
mth9
Assessment Month

Figure 4.

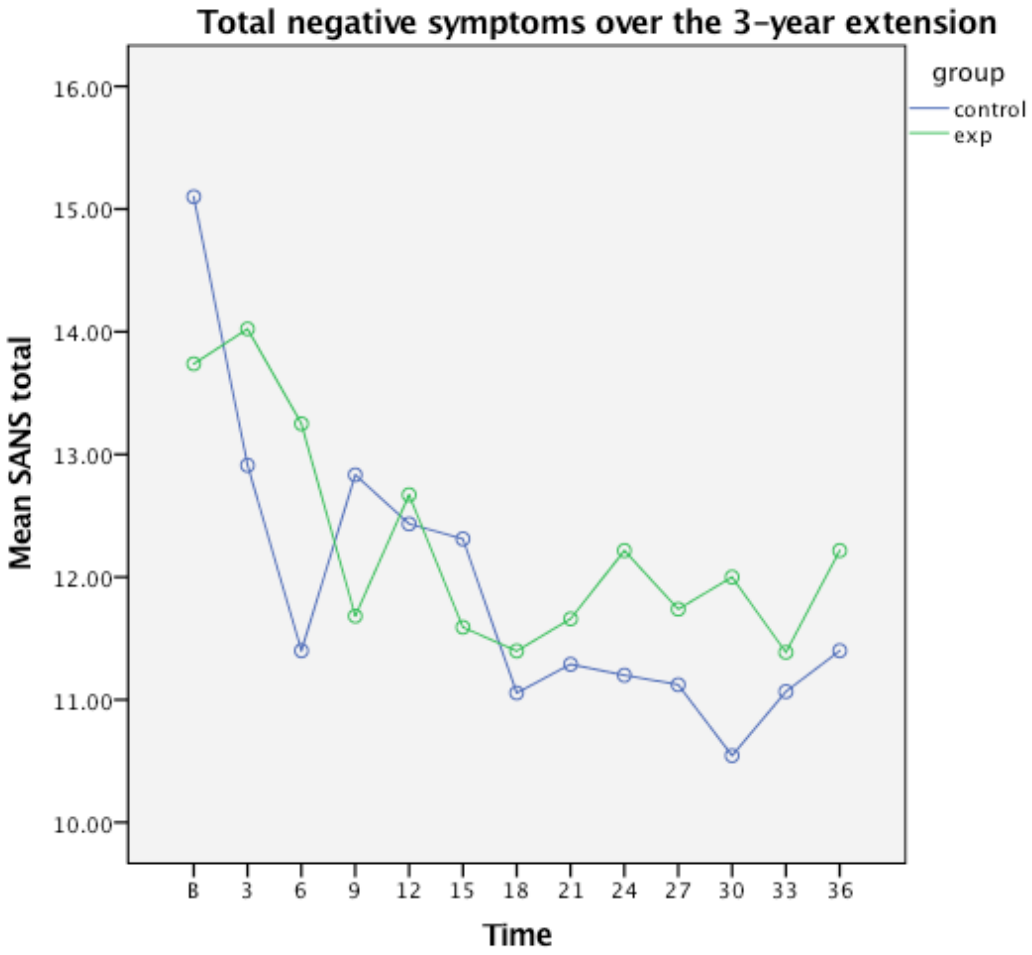

Total negative symptoms over the 3-year extension
group
control
exp
Mean SANS total
16.00
15.00
14.00
13.00
12.00
11.00
10.00
B
3
6
9
12
15
18
21
24
27
30
33
36
Time

Figure 5.

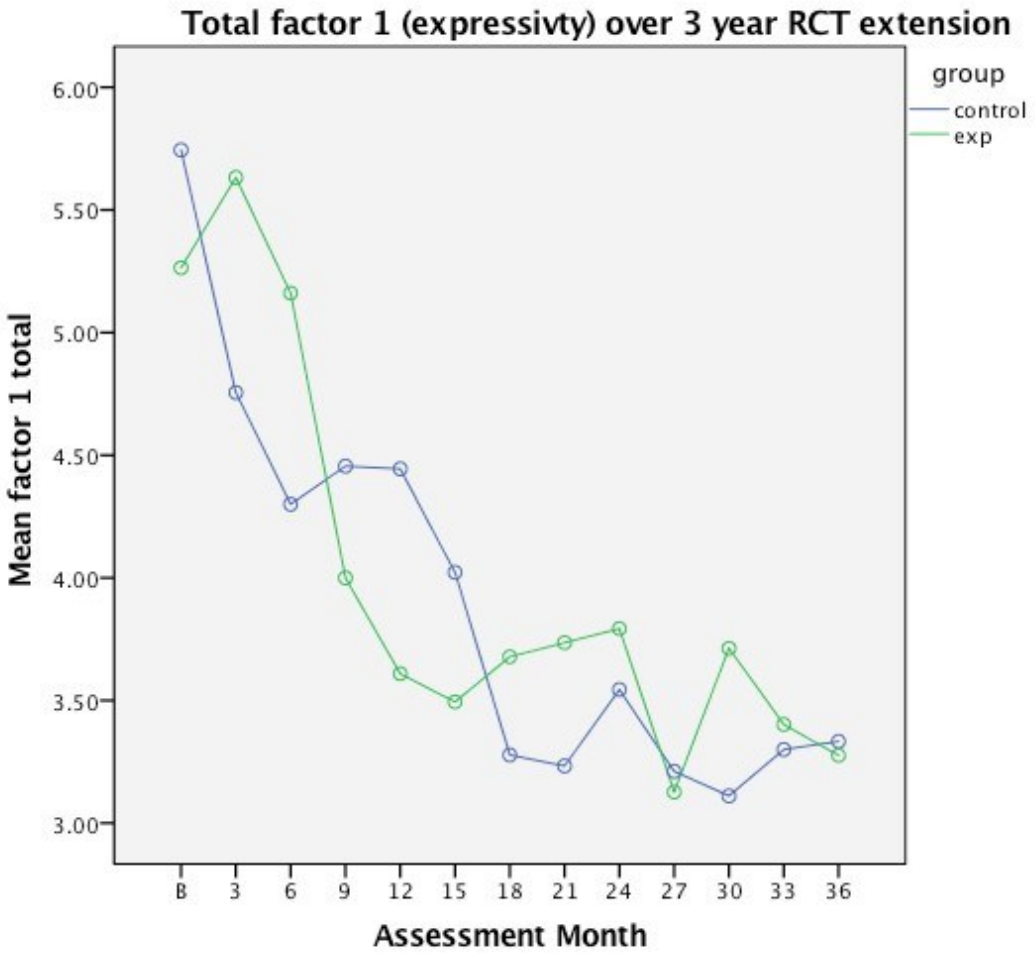

Total factor 1 (expressivty) over 3 year RCT extension
group
control
exp
Mean factor 1 total
6.00
5.50
5.00
4.50
4.00
3.50
3.00
B
3
6
9
12
15
18
21
24
27
30
33
36
Assessment Month

Figure 6.

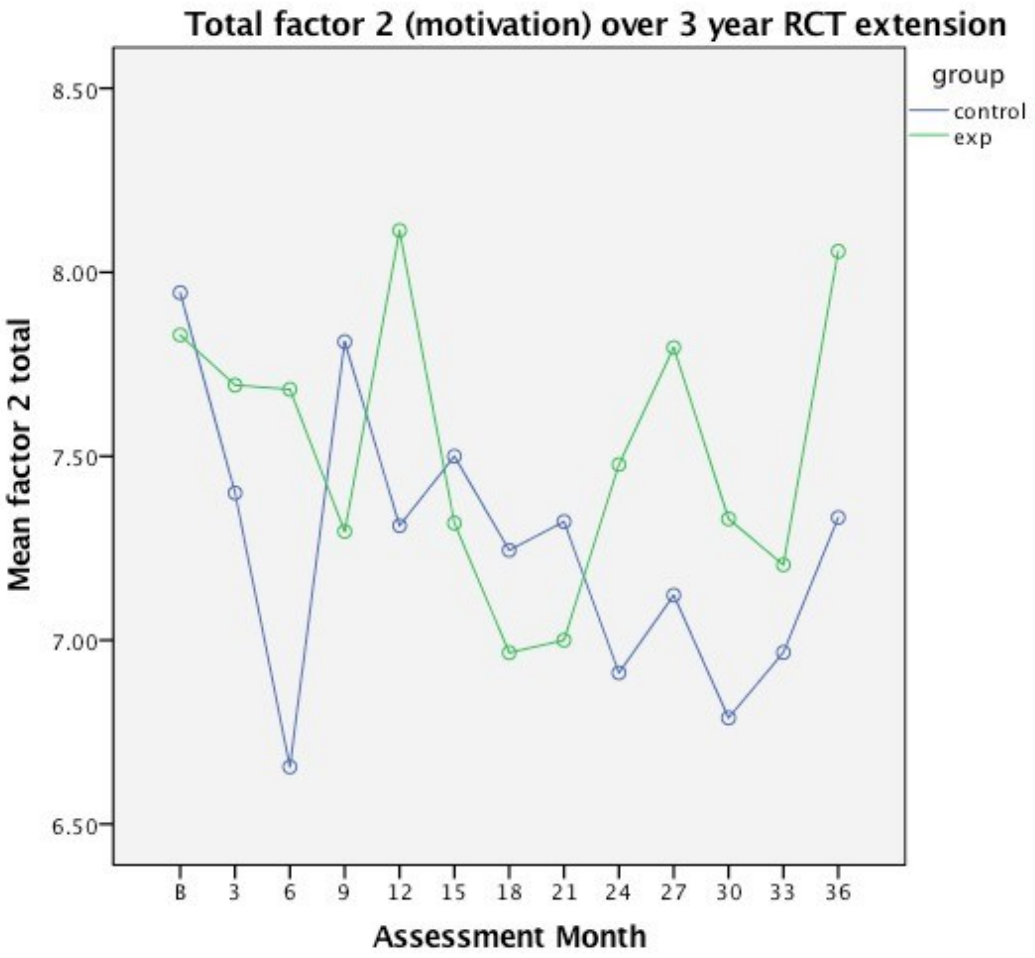

Total factor 2 (motivation) over 3 year RCT extension
group
control
exp
Mean factor 2 total
8.50
8.00
7.50
7.00
6.50
B
3
6
9
12
15
18
21
24
27
30
33
36
Assessment Month

Figure 7.

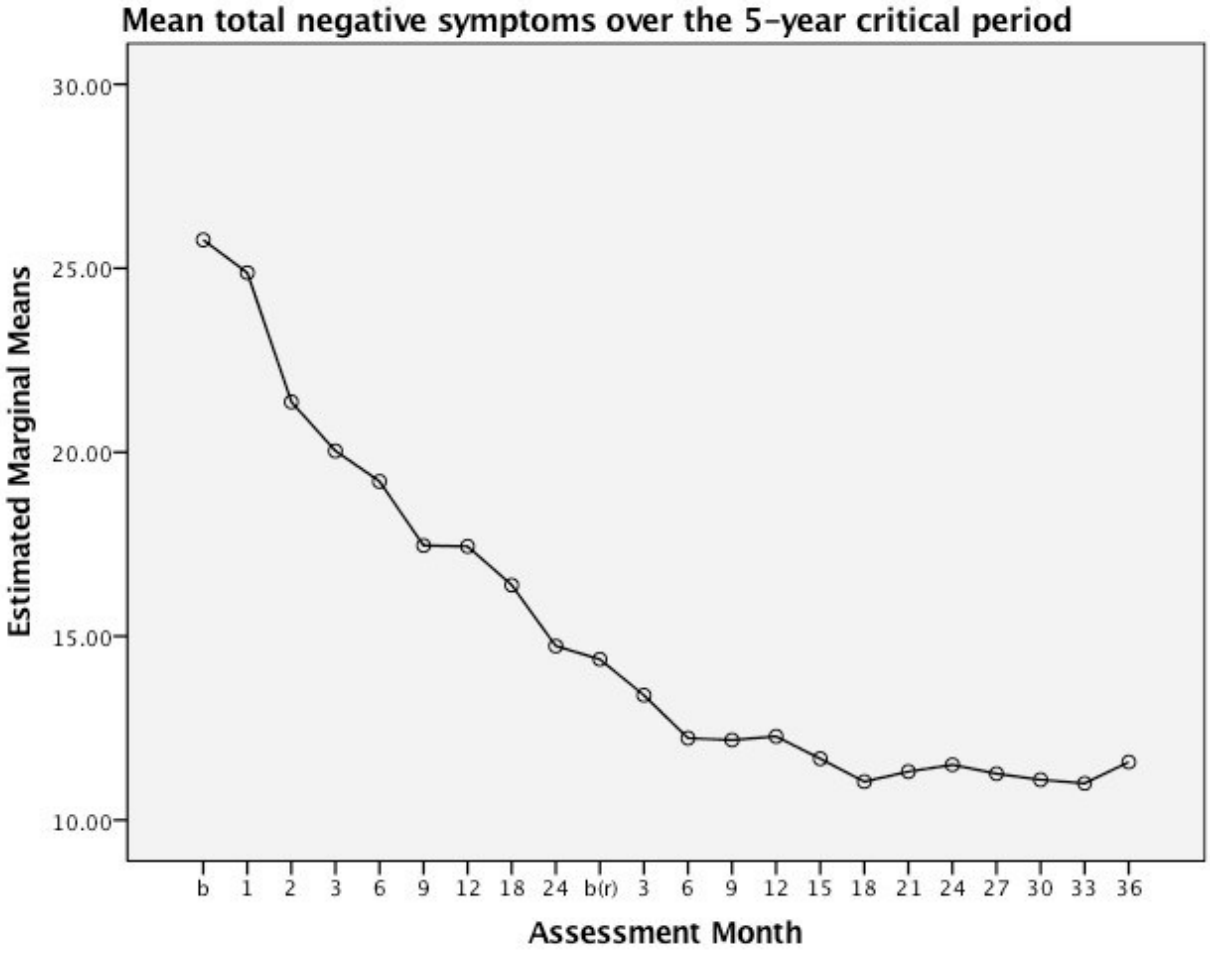

Mean total negative symptoms over the 5-year critical period
Estimated Marginal Means
30.00
25.00
20.00
15.00
10.00
b 1 2 3 6 9 12 18 24 b(r) 3 6 9 12 15 18 21 24 27 30 33 36
Assessment Month

Figure 8.

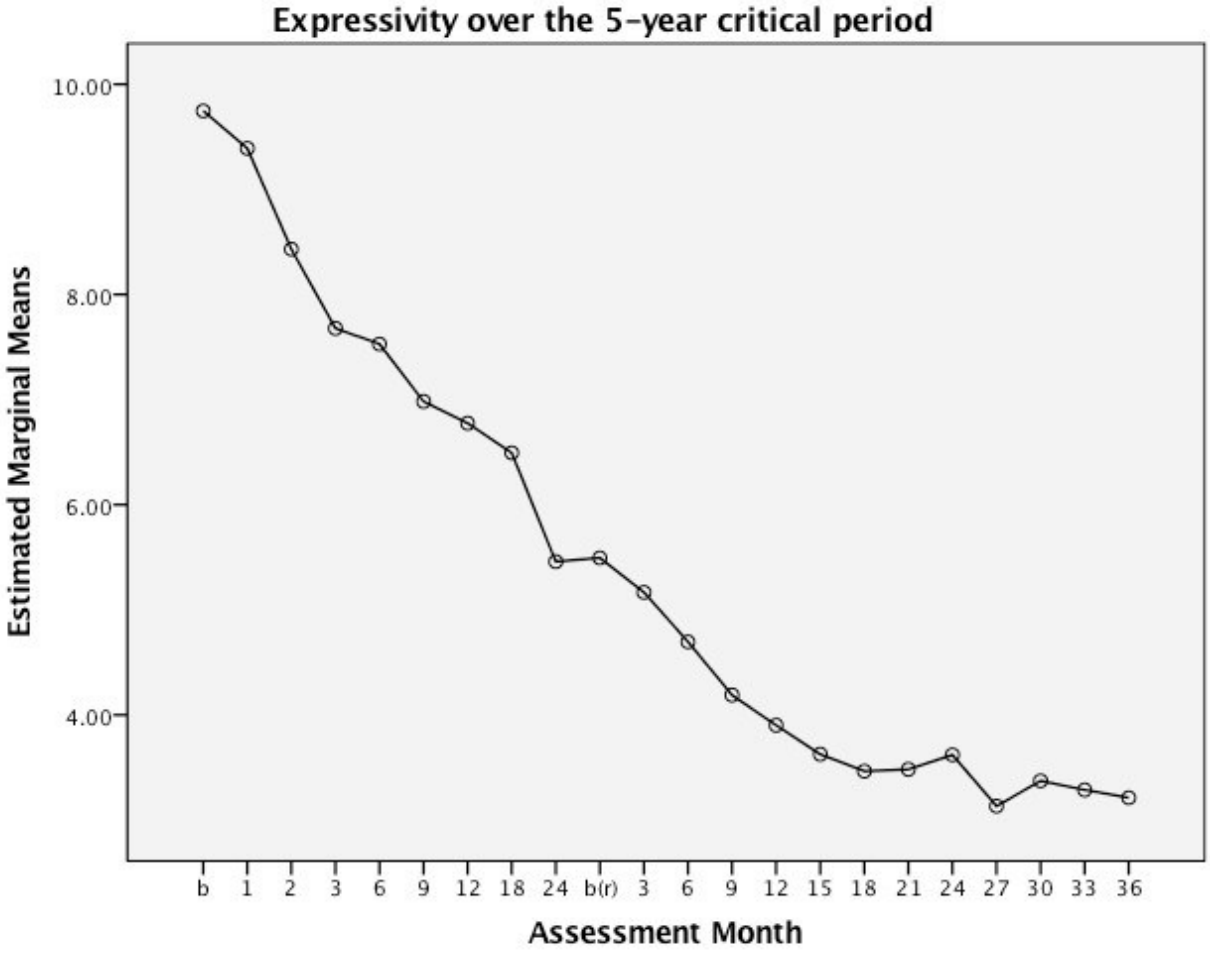
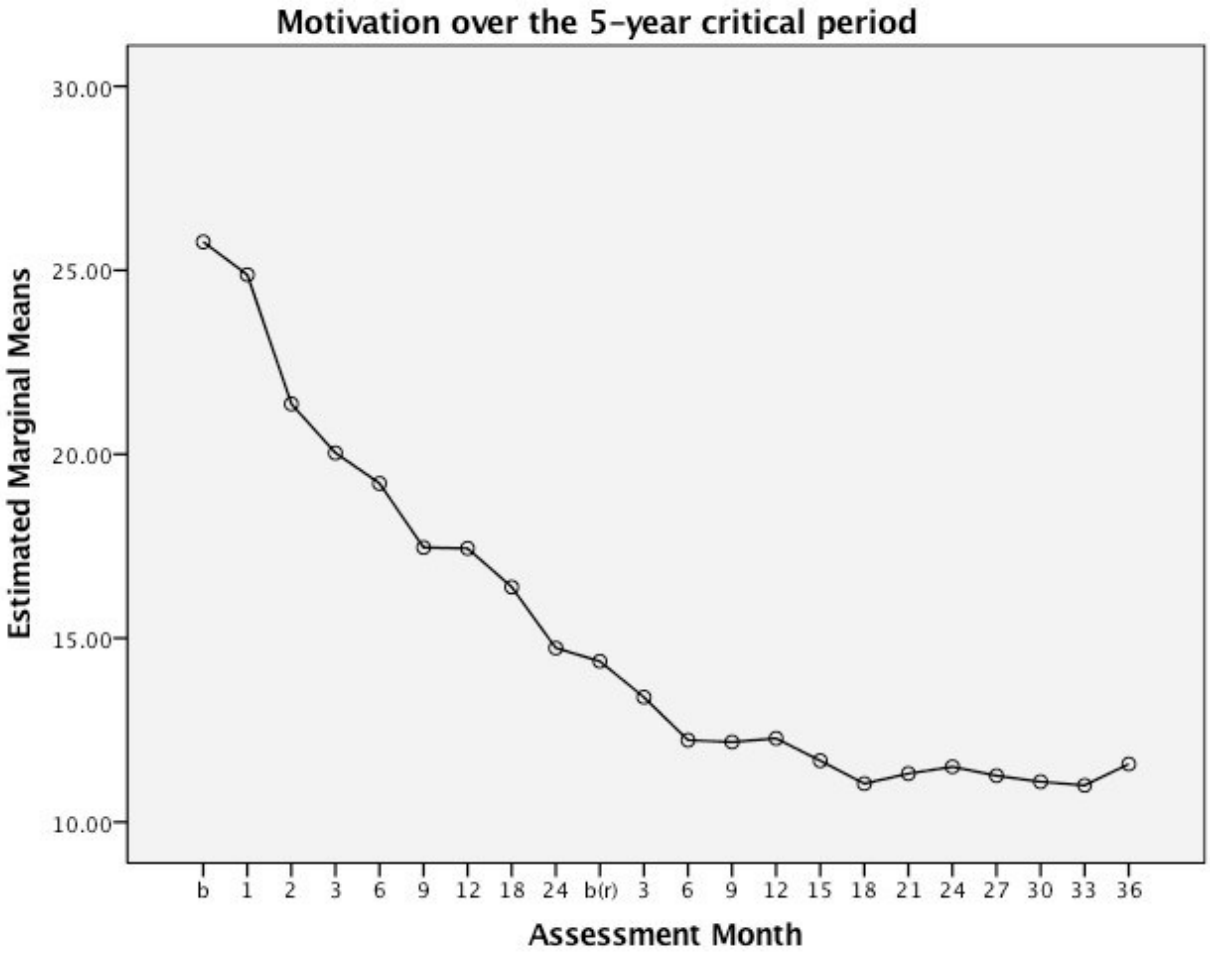

Expressivity over the 5-year critical period
Estimated Marginal Means
10.00
8.00
6.00
4.00
b 1 2 3 6 9 12 18 24 b(r) 3 6 9 12 15 18 21 24 27 30 33 36
Assessment Month

Figure 9.


Motivation over the 5-year critical period
Estimated Marginal Means
30.00
25.00
20.00
15.00
10.00
b 1 2 3 6 9 12 18 24 b(r) 3 6 9 12 15 18 21 24 27 30 33 36
Assessment Month

Discussion

Our aims were to trace the trajectory of negative symptoms in FEP within the first 2-years of initial EI service and to determine if further improvements can be made within the subsequent 3 years of the 5-year critical period and, if so, whether there is any additional benefit of EEI compared to regular care.

We confirmed previous reports of two distinct dimensions, 'expressivity' (flat Affect/alogia) and 'motivation' (avolition/asociality) that comprise negative symptoms [23, 25]. Our results show that total negative symptoms as well as individual dimensions of 'expressivity' and 'motivation' improve significantly within the first 2 years of EI. In the subsequent years, not only are gains in negative symptoms maintained, there are significant improvements in the level of negative symptoms that occur within the 3rd year. However, the latter is accounted for mainly by improvement in expressivity but not in the motivation dimensions of negative symptoms. Extended EI does not offer any advantage in the subsequent 3 years over regular care in the magnitude of improvement.

2-year outcomes

Our finding that negative symptoms decreased significantly over the first 2-years of EI is in keeping with similar studies [8, 9] including from previous cohorts within the same program [26]. Given that negative symptom change occurred gradually (with stability between months 9 and 18) over this 2-year period suggests that this improvement is unlikely secondary to change in positive symptoms as the latter often respond quickly to antipsychotic medication presented upon EI entry (see supplementary Table 1 for positive symptom change) [27]. Such results are noteworthy because negative symptoms are reported to remain relatively static over time for FEP patients in regular care [28] and few interventions are found to significantly and consistently impact negative symptoms, including interventions designed specifically to treat negative symptoms [6]. However, intervention studies for negative symptoms tend to use older patients who may be less sensitive to treatment and whose symptoms are likely to have "solidified". In comparison, our results confirm that FEP is an opportunity for negative symptom improvement when patients are

treated in EI services that are phase-specific, and treatment, including modified assertive case management, is directed towards the needs of young people [29].

3-year RCT extension

We found that EEI does not impart additional benefit on the level of negative symptoms in FEP, and that both groups improved equally for an additional 15 months, despite the continuation of psychosocial support provided only within the EI service. This lack of additional benefit provided by EEI may reflect a need for more intensive and better targeted psychological and psychosocial interventions for negative symptoms within EEI programs [7]. Our finding of parity in outcomes corroborates those from OPUS[30] where both those in EEI and regular care displayed an identical course of sustained negative symptom improvement post randomization.

Although the Hong Kong study reported a significant benefit of an additional year of EI compared to transfer into regular care, this benefit was not sustained outside of EI and both groups showed a worsening of negative symptoms at the 4th and 5th year follow-up in regular care. The discrepancy between this and our findings reported here likely represents a lower intensity of initial EI service in the Hong Kong sample. Case manager- to- patient ratio over the initial 2-years of EI in the Hong Kong study was 1:80 [12], suggesting a far lower intensity of care. Thus, patients who completed 2-years of EI within the Hong Kong program had likely not received the intensity of psychosocial intervention needed to sustain further amelioration in negative symptoms.

In the original Danish OPUS study, negative symptom gains, measured at the end of 2-years of EI treatment, were reported to have been lost at 5-year follow-up after transfer to regular care for 3-years. Neither our findings reported here nor those from the OPUS follow-up [30], both utilizing rigorous RCT methodology, substantiate the original concern that the benefit of EI, at least as it relates to negative symptoms, is lost after transfer to regular care. Further negative symptom improvement reported for both groups in our Canadian sample may be at least partially contextual. Judged in light of substantial improvements over the first 3.5 years of FEP for both groups in our study, it is likely that the initial impact of EI on patients' negative symptoms is considerable enough to propel further improvement post randomization, that is then sustained over time.

Expressivity and motivation dimensions

We found that the expressivity dimension of negative symptoms had a different course compared to the motivation dimension. The motivation dimension showed early improvement only– from entry to EI until the 9th month, before stabilizing. The expressivity dimension meanwhile showed some very early improvement over the first 2-months of entry to EI, but then settled until much later improvement, between 1.5 to 3.5 years. Differential trajectories of the expressivity and motivation dimensions in FEP over the critical period have not been reported previously. It is possible that while overall negative symptom improvement was largely independent of positive symptom remission, some aspects of motivation, particularly engagement, were more likely subsequent to control of delusions and hallucinations [31]. The lack of further improvement in motivation is concerning given evidence from previous studies that this dimension, compared to expressivity, is associated with poor social outcome [32]. On the other hand, items on the SANS measuring this dimension are assessed largely based on self-reported involvement in work and school and social relationships, which overlap with functioning [33, 34]. FEP patients who face barriers of social stigma are more reliant upon external factors such as vocational rehabilitation and other supports that are not always available [35]. Improvement in expressivity meanwhile likely represents improvement in core negative symptoms assessed based on observation during an assessment interview (flat affect and poverty of thought) and less likely to overlap with functioning or be influenced by external factors such community resources. Although it is possible that some improvement in expressivity reflects the relationship between the patient and symptom evaluator over time, less improvement post-randomization, even over 3 years of continuity with the same evaluator, suggests minimal influence of rapport. That the dimension of expressivity showed continued improvement post randomization supports findings from several studies of intact affective experience in FEP [36, 37] that may involve more internal processes including activation of the pre-frontal cortex, as recovery proceeds [38].

Our study has many strengths: we followed a cohort of FEP patients, who had little previous exposure to treatment, from the time of entry to an EI service for treatment to the end of 2 years of treatment and then for a further 3 years, thus covering the entire critical 5-year period. This provided us with an opportunity to observe possible effects of either the continuation of EI or transfer into regular care for 3 years. This study utilized a large and representative cohort of

patients and was rigorous in its design and methodology, allowing for comparisons with both Danish and Hong Kong study outcomes to map out distinct trajectories of total negative symptoms and its dimensions over time. There are, however, several limitations to this study. The first concerns the lack of a comparison control over the initial 2-years of EI. However, evidence of negative symptom remission in the first years of FEP utilizing medication alone reveal comparatively minor improvements [39] as do RCTs of regular care compared to EI [40], suggesting that improvement in the first two years may be related to the intensity and quality of an EI service. Further limitation is in regards to the number of missing observations at each assessment period post randomization. On the other hand, the large number of assessments available reflects the methodological rigour of this study which allowed us to document precise changes in negative symptoms over the full five-year critical period. All sensitivity analyses were intent to treat as per the original protocol and reconfirm our primary finding. Another limitation to this study was that we did not account for secondary negative symptoms that were the result of depression, positive symptoms or medication side effects. However, it has been shown that regardless of variations in the definition, persistent negative symptoms, that may include secondary negative symptoms, lasting for over 6-months post treatment, equally predict functional outcome [5]

Our findings add to evidence that the first 2-years of EI support critical negative symptom improvement in FEP. Post 2-years, additional gains in negative symptoms until month 15, driven largely by expressivity, are likely to occur irrespective of the type of care (EI vs regular care). While some minor improvements in the 'motivation' aspect of negative symptoms do occur later, changes are largely limited to initial EI (2 years), stressing the importance of such interventions targeting this area. Future studies may determine whether there are particular patient and caregiver characteristics associated with differential negative symptom outcomes and whether the gains achieved post 2-years of EI and then sustained at 5-year follow up are still found in the longer term.

Acknowledgments

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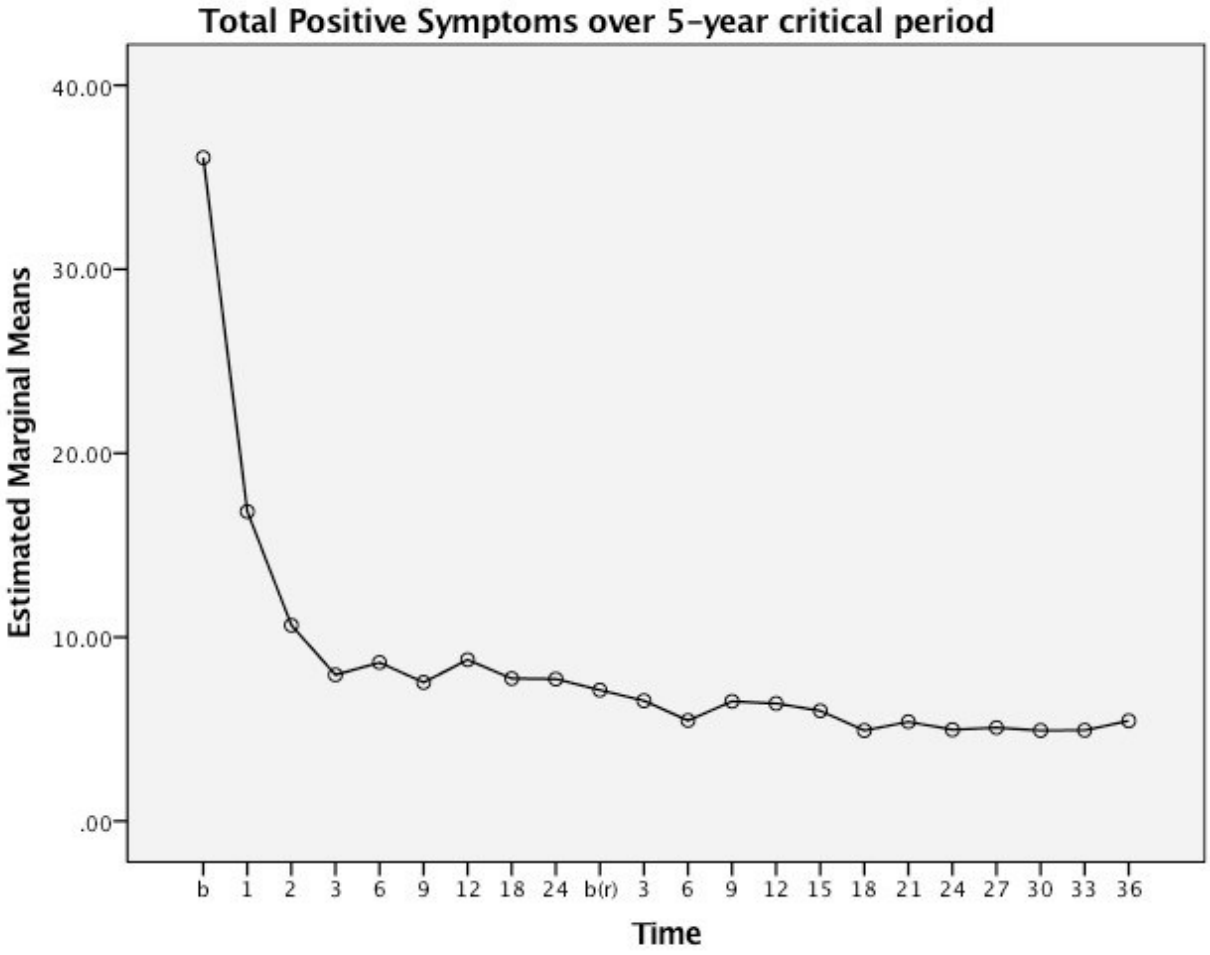
Supplementary Table 1.



7.1 Significance

There has been a strong focus on negative symptoms in psychosis as a treatment priority, largely due to its relationship with functioning and quality of life. The inclusion of negative symptoms in the definition of remission also points to the same. In the context of limited efficacy of antipsychotic medications, psychological and psychosocial interventions are the most recommended treatment add-on for negative symptoms in psychotic disorders (NICE) (Health and Excellence 2002). However, the evidence for the application of these treatments and for any comparative advantage of a particular treatment warranted exploration, as evidenced also by the survey of Canadian Psychiatrists (Chapter 2). As such, a systematic review and meta-analysis was undertaken (Chapter 3). Findings from the systematic review and meta-analysis suggest a mild to moderate effectiveness for a range of interventions, including significant effectiveness of EI on negative symptoms in FEP. However, the review also highlighted a remaining research gap regarding whether the significant effects of EI are sustainable longer term, or whether further negative symptom improvement might be made through extension of EI. This question provided the rationale for embedding such an inquiry within a protocol for an RCT (Chapter 4). The final study (Chapter 5) provides evidence on the effect and optimal duration of EI treatment for negative symptoms in FEP over two phases of initial entry into EI for 2 years, followed by either a 3-year extension of the same EI, or transfer into regular care. This data allows for a detailed mapping of the trajectory of negative symptoms throughout the first 5 years of FEP, that follows initial EI treatment. In the first phase, a naturalistic observation of negative symptoms in FEP following entry into an EI program for 2 years is presented. In the second phase, conducted

according to the RCT protocol, the answer of the optimal duration of EI treatment for negative symptoms in FEP is provided.

Through the systematic review and meta-analysis we identified a large number and range in types of interventions that are effective, albeit with only a moderate to medium effect size on negative symptom in psychosis. Results across all studies suggested that treatments that had been applied earlier were more likely to be effective than those conducted within chronic populations (Lutgens, Gariepy, and Malla 2017). Treatment in an EI service for patients in the early course of psychotic disorders was among the most significant, although the question of the optimal duration of treatment for maintaining or even furthering negative symptom gains in FEP remained. The protocol was designed with the provision for answering this question, utilizing multiple assessment points that allowed also for detailed mapping of negative symptoms over the entire first 5 years of FEP. We found substantial and significant negative symptom improvement over the first phase of analysis that encompassed the initial 2 years of EI treatment in FEP. However different longitudinal courses for the domains of expressivity and motivation within negative symptoms were discovered. While motivational deficits over phase 1 improved quickly following entry to EI, they stabilized prior to the end of the 1st year. Expressivity deficits meanwhile took longer to begin improving but continued to remit throughout the 1st phase of investigation (month 24 of year 2). Data from the RCT extension (phase 2) suggest that negative symptom improvements are not only sustained but also continue to improve for an additional 1.5 years with no comparative advantage of extended EI. We found that continued negative symptom improvement only occurred for the domain of expressivity but not for that of motivation that remained static from the 9th month onwards. Our results of no benefit of

extended EI is comparable to other most recent findings from a similarly designed trial. Continued improvement in our Canadian sample is likely to be a due to system differences.

7.2 Implications

This thesis makes several contributions to our understanding of non-biological treatments for negative symptoms in FEP. Leveraging a large body of data from almost 100 studies with negative symptom outcomes, it is clear that while psychological and psychosocial interventions have an important role as an add on treatment, alternative and more effective treatments are still needed. This knowledge may help to fuel further research into more effective interventions and may also help clinicians to be realistic about negative symptom outcomes and their slow but steady change over time. On the other hand, evidence from the first 2 years of EI both from other studies and from our own sample, show that negative symptoms can and do decrease substantially when patients are treated in an EI service. This is likely a product of the multiple targets of treatment including CBT, psycho-education and family therapy as well as intensive case management designed to provide scaffolding, support and encouragement towards recovery. Evidence from our well-designed and comparably large Canadian RCT suggests that continued improvements in negative symptoms may be expected a year and a half post EI, even after transfer into regular care. Critically, our findings over the entire 5 years show that there is a limited window for negative symptom intervention and improvements; for the dimension of motivation is even further narrowed to include only the first two years of EI intervention. To take advantage of this opening as a critical opportunity, treatments for negative symptoms should be applied within the early course of psychosis and within an EI service where the quality and

combination of psychosocial interventions are most likely to be available. Hence, findings outlined are further evidence that EI services are beneficial for patients with FEP.

7.3 Limitations

There are several limitations to the work presented in this thesis. Despite preparing strategic search constructs, it is likely that some studies with negative symptom outcomes in psychosis were not detected and therefore excluded in our analysis (Cella et al. 2017). This is to be expected from all systematic reviews and meta-analyses of this size that are likely not exhaustive. As search terms that are too general are likely to procure too many non-relevant studies, the balance is on creating terms that are wide enough to capture the majority that are applicable. It is of note however, that our review was large and contained studies published across many years and from a wide array of intervention, including more obscure treatments (pet therapy, dance etc). As well, this review did not separate primary from secondary negative symptoms nor were symptom domains explored. Given that most studies were not designed to investigate negative symptom outcomes such data was largely unavailable. However, it remains that this systematic review and meta-analysis is extensive and comprehensive in its approach to reviewing and comparing non-biological treatments for negative symptoms.

In hindsight, one of the limitations of the rigorous RCT methodology was the difficulty in maintaining continuous (every 3-months) and long-term contact with patients over the entire 3-year trial extension. On the other hand, a larger number of patients were recruited to control for dropouts and intention to treat analysis was pre-planned. The final thesis manuscript was limited in that it did not explicitly delineate between primary and secondary negative symptoms.

However, post hoc analyses alongside a comparison of negative symptom and positive symptom curves indicates that they are independent of each other. Missing data was balanced by the large number of assessments conducted per patient and by intention to treat analysis that showed the same outcome as analysis using imputed data. It is crucial to consider that our findings of the trajectory of negative symptoms are limited to the context of the availability and effectiveness of an initial 2 years of EI in FEP.

7.4 Future studies

Negative symptoms remain a critical target for treatment in psychotic disorders. Despite the improvements seen in FEP up until the 3rd year, mean total negative symptoms likely still represent obstacles in functioning. Future studies could investigate the 2 dimensions of negative symptoms independently and treatments needed to target motivation directly may influence functioning. Disentangling primary from secondary negative symptom improvements may also provide a better understanding as to how interventions are effective.

While our findings suggest an even shorter window of change for motivational compared to expressive deficits, it is not clear if that range of time simply begins earlier on. Motivational deficits in individuals at 'clinical high risk' for psychosis (Schlosser et al. 2014; Cannon et al. 2008) seen even prior to onset of syndromal level psychosis, may be detected and targeted even earlier. As we do not yet understand the biological and psychosocial origin of negative symptoms and, particularly of expressive and motivational deficits that are likely to better represent the underlying structure of such symptoms, it is important to clarify the possible role of

social barriers such as stigma to social and vocational isolation. Future studies may better disentangle motivational deficits from lack of economic opportunity and from stigma that may serve as a barrier to integration and independence. Studies that correlate early life experiences with particular domains of negative symptoms may serve to better understand not only their emergence but their treatment. Qualitative studies may be utilized to this end.

Not withstanding all that may be improved in research and treatment of negative symptoms, findings from this thesis suggest that there is reason for optimism in FEP and that EI is a critical component to securing a brighter future for young people entering treatment for their FE of psychosis. Substantial improvements in negative symptoms that are made over EI are also sustained in the long term, allowing for better life-long functioning and overall trajectories.

Appendices

Appendix A: Table 1

Table 1: Negative symptom items and their clinical manifestations according to 4 symptom scales

SANS	NSA	PANSS –Negative symptom subscale	CAINS
Affective flattening	**Affective dysfunction**	Blunted affect	**Expression**
Unchanging expression	Reduced range of emotion		Facial expression
Decreased movements	Reduced modulation of affective intensity		Vocal expression
Paucity of gestures	Reduced display of affect on demand		Expressive gestures
Poor eye contact			Quantity of speech
Affective nonresponsivity			
Inappropriate affect			
Lack of vocal inflection			
Alogia	**Dysfunction of communication**	Lack of spontaneity and flow of conversation	
Poverty of speech	Prolonged time to respond	Stereotyped thinking	
Poverty of content	Restricted speech quality		
Blocking	Impoverished speech content		
Increased latency response	Inarticulate speech		
Avolition/apathy	**Dysfunction of motivation**		**Motivation and pleasure**
Poor grooming/hygiene	Poor grooming/hygiene	Emotional withdrawal	Close family/spouse/partner relationships
Impersistance at work/school	Reduced sense of purpose	Passive apathetic social withdrawal	Close friendships and romantic relationships
Physical anergia	Reduced hobbies and interest		Frequency of pleasurable social activities
	Reduced daily activity		Frequency of expected pleasure from social activities
Anhedonia/asociality	**Social dysfunction**	Poor rapport	Motivation for work and school
Few recreational activities	Reduced social drive		Frequency of expected pleasure from work and school
Decreased sexual interest	Reduced sexual interest		Motivation for recreational activities
Decreased capacity for closeness	Poor rapport with interviewer		Frequency of pleasurable recreational activities
Few friends/prefers isolation			Frequency of expected pleasure from recreational activities
Attentional impairment	**Motor retardation**	Difficulty in abstract thinking	
Social inattentiveness	Reduced expressive gestures		
Inattentiveness on mental status examination	Slow movements		

Modified from: Stahl & Buckly,2007; Foussias & Remington 2008; Kring et al., 2013

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