CHILDREN'S MENTAL HEALTH
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Early Psychosis: A Review of the Treatment Literature

A Research Report Prepared for the
British Columbia Ministry of Children
and Family Development

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PREFACE

This is one in a series of research reports being prepared by the Children's Mental Health Policy Research Program at the University of British Columbia at the request of British Columbia's (BC's) Ministry of Children and Family Development (MCFD). At any given time, over one in seven or 140,000 children in BC experience mental disorders serious enough to impair their development and functioning at home, at school and in the community.[1] MCFD has made it a goal to improve children's mental health in BC. In 2003, MCFD announced a new *Child and Youth Mental Health Plan* (the *Plan*) to better address the needs of children and families in BC.[2]

The research reports developed through Children's Mental Health Policy Research Program will support MCFD's *Plan* by identifying the most effective prevention and treatment approaches available for a variety of children's mental health problems. This report focuses on early psychosis and is intended to assist MCFD to provide quality services to young people and their families so that positive outcomes may be maximized for those affected by the early stages of psychotic disorders. Other reports have focused on conduct disorder, on First Nations children's mental health, and on anxiety. Future reports will cover depression, eating disorders, co-morbidity, attention problems, other mood and developmental problems, suicide prevention, knowledge exchange, parenting and service models. These reports will be a resource for policy-makers, practitioners, families, teachers and community members working with children in BC. We recognize that research evidence is only one component of good policy and practice. This report addresses only the content, or the specific factors, in treatment modalities for early psychosis. This should not be interpreted as a failure to recognize the importance of the therapist's experience, clinical judgment and other non-specific factors that are beyond the scope of this report. Our goal is to nevertheless facilitate evidence-based policy and practice by making summaries of the best research evidence available to everyone concerned with improving the mental health of young people in BC.

EXECUTIVE SUMMARY

Psychosis is a serious public health issue that can lead to severe long-term disability. A new paradigm has emerged in the past decade that aims to decrease the pain and risks associated with psychosis and optimize the chances of a successful recovery. Despite over 100 years of research, understanding of the causes of schizophrenia, schizoaffective disorder, bipolar disorder and the other disorders associated with psychosis remains limited. Although successful treatments have been developed, extrapolation of the research findings from populations with chronic disorders should not be assumed uncritically. This report reviews research on the best interventions currently employed for early psychosis, which usually manifests in young people.

Findings

- Antipsychotic medications are effective for both acute treatment and maintenance. The newer atypical antipsychotics are more efficacious and enjoy a more favorable side effect profile than older antipsychotics. Weight gain is a concern with several of the atypical antipsychotics.
- Family interventions have been shown to improve several outcomes.
- While the controlled research on cognitive behaviour therapy, psychoeducation and other psychosocial interventions in early psychosis is limited, research from the general literature and from less well-controlled studies supports their use.
- Evidence from specialized early psychosis programs suggests improvements over standard treatment.
- Research findings on prevention of psychosis or the ability of interventions to prevent onset during suspected initial prodromes is at best equivocal.

Recommendations

- Atypical antipsychotic medications are effective for acute psychoses. Antipsychotic doses should be low and titrated slowly. The use of multiple antipsychotic medications is not usually warranted. Clozapine should be reserved for treatment refractory cases.
- Lithium remains the first line mood stabilizer when mania accompanies psychotic symptoms.
- Family involvement/interventions are recommended.
- Cognitive behaviour therapy is advised on the basis of limited support in the first episode literature and considerable support from the general schizophrenia and affective disorder literature.
- Psychoeducation receives substantial support in the general literature yet has been infrequently studied in early psychosis despite being an integral component of most programs. Psychoeducation is recommended for all cases.
- Interventions currently used in treating first episode cases are not recommended for use in suspected onset-prodrome cases. Further research on improving the identification rate must be coupled with rigorous treatment trials.
- Current early psychosis guidelines are consistent with the ethics and theoretical framework of the early intervention paradigm and represent an array of interventions that are often embodied in specialized programs. No evidence to date suggests these programs represent an inferior option compared to more traditional treatment approaches. Despite a lack of statistical power, several studies demonstrated clear advantages to integrated programs over standard care. The individual components of these programs that contribute to good outcomes needs further study.
- More research is needed on specific interventions, on mixed interventions embodied in programs, and on prevention approaches. In particular, studies of the effectiveness of psychoeducation and group versus individual therapies are of high priority and must be done using sufficiently sized samples. Outcomes measured should be multidimensional and include quality of life, cost effectiveness and psychosocial functioning. Comparisons both between the atypicals and relative to mood stabilizers and first generation antipsychotics are needed in both affective and nonaffective psychoses. Studies must move beyond short-term evaluation (e.g., less than one year) to ascertain whether early intervention significantly alters the course of disorders over many years.

1 INTRODUCTION

1.1 Defining Early Psychosis

Psychotic conditions are a major public health concern. Persons with psychosis may engage in actions that are dangerous to themselves and others. Onset in late adolescence and early adulthood causes major disruptions in the ability of individuals to meet developmental tasks. Social, sexual, academic and vocational challenges may be threatened as are consolidation of personal independence, identity and values. Individuals experiencing psychoses are more prone to suicide, depression, anxiety, aggression, substance abuse, cognitive impairment, victimization, poverty and increased medical problems.[3,4] When psychosis occurs, family and other social relationships suffer, and the family experiences significant distress.[5]

The most common diagnoses associated with psychosis are schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder, and major depression with psychotic features. Most psychotic disorders tend to follow a relapsing course wherein periods of acute psychosis are preceded by periods of disruption (a "prodrome") and followed by recovery, deterioration, and subsequent re-emergence of florid psychosis. Conceptualizing the disorder as consisting of these phases suggests that different strategies become appropriate for assessment and treatment at each stage.[6]

Outcomes for psychotic disorders are generally disheartening. A recent epidemiological outcome study reported that three quarters of first episode patients with schizophrenia and almost half of those with non-affective psychoses were receiving work disability benefits after five years.[7] Nine per cent of the schizophrenia patients and 39 per cent of the non-schizophrenia patients were rated as not being in need of treatment. Schizophrenia is associated with poorer functional outcomes and slower recoveries from episodes than other psychotic disorders.[8,9] Bipolar disorder is a prototypical relapsing-remitting psychiatric disorder. Lifetime prevalence is about 1.6 per cent.[10] Patients who have ever been hospitalized are expected to spend about 20 per cent of their lifetime in episodes (starting from the onset of their disorder).[11] Two years after an initial episode of mania, 72 per cent achieved syndromal recovery but only 43 per cent attained functional recovery.[12] Finally, major depression accompanied by psychosis leads to poorer five- and 10-year symptomatic and functional outcomes compared to non-psychotic depressions.[13] For all psychotic disorders, the better the short-term course, the better the long-term outcome with the percentage of time spent with psychotic symptoms in the first few years being the best predictor.[8]

1.2 Rationale and Goals of Early Intervention

Many studies have found long delays before treatment began in first-episode psychoses, including bipolar disorder.[14] Long durations of untreated psychosis have been associated with slower and less complete recovery, more biological abnormalities, more relapses and poorer long-term outcomes.[15-17] Assessment and treatment procedures were often experienced by clients as traumatizing, alienating, age-inappropriate and inconsistently applied over time.[18]

The early phase of psychosis, the period when most deterioration occurs, may represent a "critical period" for determining long-term outcome.[19] This period may present an important treatment opportunity because course-influencing biopsychosocial variables, including patient and family reactions, develop and show maximum ability to positively change during this time.[20]

Early intervention in psychosis aims to achieve:

- better short- and long-term prognoses
- increased speed of recovery
- lower use of hospitalization
- reduced secondary psychiatric problems (e.g., depression, substance abuse, etc.)
- preservation of personal assets, psychosocial skills, role functions, family functioning and social/environmental supports

Achieving these goals entails:

- providing age-appropriate support to minimize disruption in the lives of these individuals and enable them to more successfully meet their developmental challenges
- limiting the suffering and possible negative repercussions of psychotic behaviour through improving early recognition and rapid appropriate response
- involving and assisting families
- adopting a wide range of treatment targets
- remaining sensitive to factors that may hinder successful ongoing treatment, such as
  - negative effects generated by aversive procedures
  - medication side effects
  - discontinuities in care
  - stigma and other impediments to collaborative relationships

1.3 Interventions in Early Psychosis

The goals of early intervention in first episode psychoses necessitate the implementation of a broad biopsychosocial approach. The development of innovative approaches is demanded by the diagnostic uncertainty inherent in many early phase disorders, and by the goals of providing intensive and continuous care, family involvement, age- and stage-appropriate services, and liaison with school, work and community services. Furthermore, careful attention to co-morbid psychiatric and social problems, rapid reintegration and relapse prevention are formidable challenges. Most existing mental health services have not been developed to provide the type of care envisioned in the early intervention paradigm. Evaluation of these services is in its infancy. Many of the treatments for psychotic disorders are conducted and researched using populations with chronic illness and are reflected in the practice guidelines published for most disorders.[21,22] Although efficacy has been established in many realms, the assumption that these treatments will always be appropriate and effective in early psychosis cases is equivocal. The only widely published guidelines expressly directed at early psychosis are predominantly clinically derived.[23]

Early psychosis intervention also must account for significant variation in disorders, cultural differences and service delivery systems while retaining consistency in the operationalization of theoretical and ethical underpinnings. This review will not address all of the clinical concerns that arise because of this diversity. Nor will it address service delivery issues such as models, structures, professional staffing and health economics. Rather, attention is focused on research pertaining to those interventions that are widely employed.

2 METHODS

2.1 Scope

For the purpose of this report, early psychosis was defined as a five-year period following a first episode of either non-affective or affective psychosis that occurs in individuals during adolescence or early adulthood. The review focused on studies investigating the effects of early psychosis programs, treatments, and prevention efforts on clinical outcomes considered to be core features of early psychosis.

Issues not considered central to this review include:

- populations with longstanding or chronic psychotic disorders
- populations with very early or late onset psychosis
- service delivery matters in isolation from specific interventions (e.g., case management models and organizational issues)
- interventions focused solely on treatment of secondary effects of either psychosis or treatments for psychosis (e.g., interventions for substance abuse in psychosis or interventions for medication side effects)

2.2 Search Methods

Searches were performed using several databases including Medline, PubMed, PsychINFO and the Cochrane Collaboration Database.

TABLE 1. Search Terms

Early Psychosis	Treatment-Pharmacotherapy	Treatment-Psychosocial Interventions	Programs	Prevention/ Prodromal Intervention
• early • first-episode • recent-onset • adolescent • adolescence *in conjunction with diagnostic terms:* • psychosis • psychotic disorder • schizophrenia • schizoaffective • schizophreniform • depression • bipolar disorder • mania • manic	• antipsychotic agents • antimanic agents • drug therapy or treatment or intervention *combined with early psychosis terms*	• psychosocial • cognitive • behaviour • group • family *combined with:* • therapy • treatment • intervention *or* • psychotherapy • patient education • psychoeducation *combined with early psychosis terms*	• evaluation studies *combined with early psychosis terms* *or* *all known early psychosis program names* (e.g., EPPIC, TIPS, PEPP)	• at-risk mental state • prodrome • prodromal *or* • high risk • at risk *in conjunction with diagnostic terms* *combined with:* • prevention • intervention and pharmacotherapy, psychosocial treatments and program terms

Where possible, search terms were matched with subject headings and searched as keywords. Search terms were modified according to the database searched.

Searches were done broadly without limits other than "English Language" and "Human Subjects." All abstracts obtained through these searches were assessed for interventions or prevention studies with clinically relevant outcome measures (either original study or review) within early psychosis. In order to ensure that all studies with the highest level of evidence were included, searches were rerun with the limit "Randomized Controlled Trial" and crosschecked. Review papers and book chapters were hand searched to identify any additional studies. Finally, the manufacturers of the three atypical antipsychotic medications used in early psychosis in BC were contacted and kindly provided references regarding their respective medications.

Articles retrieved were reviewed for inclusion according to the following criteria:[24]

TABLE 2. Inclusion Criteria

Basic Criteria
- Original or review articles in English about humans
- About topics relevant to children's mental health in BC communities

Reviews
- Clear statement of relevant topic
- Clear description of the methods including sources for identifying literature reviewed
- Explicit statement of criteria used for selecting articles for detailed review
- At least two studies reviewed met criteria for assessing original research studies

Research Studies
- Clear descriptions of participant characteristics, study settings and interventions
- Diagnostic "gold" standard for early psychosis or at-risk mental state
- 50% or more of participants were in their first or second episode or within the first five years of illness
- Random allocation of participants to comparison groups
- Double-blinding procedures for medication studies
- The criterion of 80% completion rate for interventions was relaxed because it would have excluded most pharmacotherapy trials and studies that depended on long follow-up periods. Completion rates reported in individual studies are cited in the tables.
- Outcome measures of both clinical and statistical significance (response criteria in pharmacotherapy trials was typically defined as a 40% or 50% drop in score on standardized symptom rating scales and/or ratings of much or very much improved overall)

Studies were reviewed starting with those that had the highest level of evidence available (i.e., studies that had random allocation of participants to comparison groups). For topics where this level of evidence was not available, non-randomized studies with a comparison group were reviewed. Controlled trials were outlined in tables and discussed first. Where there was insufficient data from controlled trials, evidence from uncontrolled trials in early psychosis was discussed. Where this data was lacking, discussion turned to the general literature on long-standing psychotic disorders. Disagreements about which articles to include were resolved by consensus involving all the authors.

TABLE 3. Studies Included

	Number of Articles Retrieved and Assessed	Number of Studies Represented in Tables
Pharmacotherapy	50	13
Psychosocial Interventions	47	12
Programs	19	6*
Prevention	5	2

* Refers to programs (not studies) represented.

3 PHARMACOTHERAPY

Randomized Controlled Trials

Pharmacotherapy is the most researched intervention in early psychosis. Table 1 summarizes the 13 randomized controlled trials addressing first episode psychosis done to date. Most samples consisted of patients with schizophrenia spectrum disorders with only two studies using exclusively bipolar patients. Most studies were short term (e.g., 5-12 weeks) and examined symptomatic reduction efficacy and safety.

The available evidence suggests that the atypical antipsychotics are at least as efficacious as typicals in decreasing psychopathology. In all studies the percentage of patients who met response criteria was higher with the atypicals. The atypicals also showed several advantages regarding side effects with the exception of greater weight gain. Dropout rates were lower for atypical antipsychotics, which suggests better tolerability of these medications. Several studies found that low doses were preferable to high doses. Two trials that studied relapse rates (Crow;[25] Kane[26]) showed efficacy of typicals versus placebo in preventing relapse. The one-year clozapine study showed equal efficacy to chlorpromazine but greater speed of recovery with clozapine. Quicker response time was also found for risperidone and olanzapine versus haloperidol (Sikich[27]). The evidence for the use of mood stabilizers is limited with one trial (Geller[28]) showing lithium reducing substance abuse (but not mood symptoms) in bipolar disorder patients more than placebo. A second showed that quetiapine appeared to boost the effectiveness of divalproex in treating manic symptoms.

One further double-blind study was not included in the table because it focused on very treatment refractory patients with early onset schizophrenia.[29] This study found that clozapine showed several advantages over haloperidol in treating symptoms of psychosis.

Other Evidence

The volume of research specific to first episode psychosis considerably lags the number of studies published on long standing affective and non-affective disorders. The assumption that studies using established illness may be extended to earlier phases of illness and younger patient populations has been adopted frequently in clinical practice. However, this practice may not be wholly defensible on empirical grounds. The efficacy of the atypical antipsychotics for the treatment of acute episodes of schizophrenia and mania has considerable support from randomized controlled trials, systematic reviews and meta-analyses.[30-32] The clinical efficacy of olanzapine, risperidone, clozapine, amisulpride and quetiapine are well documented compared to typical antipsychotic medications. The efficacy of antipsychotics in schizoaffective disorder has also been confirmed.[33] The available evidence suggests that treatment of schizoaffective disorder with both a mood stabilizer and antipsychotic may be optimal although further research on maintenance therapy is especially needed.[34]

Despite this body of research, direct transfer of findings to first episode patients is not always appropriate. For example, the doses used in efficacy studies was often much higher than those found to be optimal in first

episode cases[35-37] and younger populations appear to be more susceptible to side effects.[27] Clozapine, the gold standard medication for treatment resistant schizophrenia, has not been shown to confer benefit over other antipsychotics in treating first episode schizophrenia or schizoaffective disorder.[38]

The studies in the pharmacotherapy table also show that typical antipsychotic medication helps prevent relapse in early phase schizophrenia. Studies regarding the atypicals and relapse are limited to established illness. Systematic reviews and meta analyses have concluded that, compared to typicals, relapse rates were modestly but significantly lower with the atypicals.[39]

Medication nonadherence is a common problem in affective and non-affective psychoses. In first episode cases followed for one year, about 40 per cent were adherent, 20 per cent inadequately adherent and 40 per cent nonadherent with younger age, poorer premorbid functioning, substance use and younger age at onset being significant predictors on nonadherence.[40] Relapse when medication is withdrawn after remission of the initial episode of schizophrenia is common.[41] In light of the fact that many patients are nonadherent and that about 20 per cent of patients with schizophrenia will not have another episode,[42] an approach called intermittent targeting is being evaluated.[43] In this approach, medication is withdrawn under close monitoring conditions and is restarted at the earliest signs of deterioration. One study of medication withdrawal in remitted first episode schizophrenia patients found that when symptomatic exacerbation was used as a criterion, 96 per cent relapsed within two years.[44] However, when rehospitalization was used as a criterion, the relapse rate fell to 13 per cent. These results and others[43] suggest that intermittent targeting can be a useful approach for patients who no longer take antipsychotic medication.

Finally, numerous controlled studies have now been conducted that show the atypicals exert positive effects on the cognitive dysfunctions found in schizophrenia spectrum disorders.[45] This may prove to be especially important since neurocognitive deficits have been associated with poorer functional outcomes.[46,47]

Side Effects of Antipsychotic Medications

- *Motor* – The rates and severity of extrapyramidal side effects are considerably lower with atypical medications as shown in the table and via other studies in established illness samples.[32,48-50]
- *Cardiac* – Although the potential for cardiac abnormalities (torsade de pointes) resulting in sudden death has been confirmed for the typical antipsychotics, no association has been found with olanzapine, risperidone and quetiapine.[51]
- *Weight gain* – Weight gain is associated with the atypicals but a large variation exists with clozapine and olanzapine producing the most and ziprasidone producing the least.[52]
- *Diabetes* – A study of 38,632 patients in the United States found that, after controlling for age, patients who received an atypical antipsychotic had a nine per cent greater chance of developing diabetes compared to those who receive a typical antipsychotic.[53]

Pharmacotherapy of Affective Psychoses

Table 1 showed that little research has been published regarding the most efficacious treatments for affective disorders that present with psychotic features. Lithium is an established treatment and quetiapine was shown to assist in the reduction of manic symptoms when added to lithium. Traditionally, lithium and divalproate have been considered first line treatment for acute and maintenance treatment.[22,54] More recently, randomized controlled trials using populations with established illness have demonstrated the efficacy of atypical antipsychotics in acute mania as both monotherapy and adjunctive to "mood stabilizers.[55,56]

Maintenance therapy for bipolar disorder with antipsychotic medication has begun to receive some support from controlled trials[55] both as monotherapy and as adjunctive therapy.[57] The optimal time period for which antipsychotic medication should be continued in remitted bipolar patients presenting with psychosis remains to be determined.[58]

TABLE 4. Pharmacotherapy for Early Psychosis

Study	Sample	Design	Intervention	Findings
Crow, MacMillan, Johnson et al.[25] (UK)	• n = 120 • *Age:* 15-70 years (74% under 30) • *Sex:* 62% male • *Ethnic Majority:* Caucasian (69%) • *Diagnosis:* nonaffective psychoses • *Other Information:* First episode	• *Comparison Group(s):* Placebo (n = 66) • *Drop-out Analyses:* Listwise	• Typical antipsychotics (n = 54) – variable dose range • Provided for 2 years	• 89% of sample completed intervention • 1-year follow-up: Lower relapse rates in antipsychotic vs. placebo group (38% vs. 63%) • 2-year follow-up: Lower relapse rates in antipsychotic vs. placebo group (58% vs. 70%) • Overall, longer DUPs associated with higher risk of relapse
DeHaan, van Bruggen, Lavalaye et al.[65] (Holland)	• n = 24 • *Age:* 17-28 years • *Sex:* 96% male • *Ethnic Majority:* Not reported • *Diagnosis:* Schizophrenia (100%) • *Other Information:* First (83%) or second episode	• *Comparison Group(s):* Haldol (n = 12) – fixed dose = 2.5 mg/day • *Drop-out Analyses:* Pre post listwise	• Olanzapine (n = 12) – fixed dose = 7.5 mg/day • Provided for 6 weeks	• 75% of olanzapine and 92% of haldol group completed intervention • No group differences in psychopathology, subjective well-being, or side effects • Overall, significant improvement on global measure of illness severity (no group differences) • D2 receptor binding (between 60-70%) was associated with better subjective experiences

TABLE 4. Pharmacotherapy for Early Psychosis, continued

Study	Sample	Design	Intervention	Findings
Delbello, Schwiers, Rosenberg et al.[64] (US)	• n = 30 • *Age:* 12-18 years • *Sex:* 53% male • *Ethnic Majority:* Caucasian (83%) • *Diagnosis:* Bipolar disorder (47% with psychosis)	• Stratified by psychosis and sex • *Comparison Group(s):* Placebo + divalproex (DVP; n = 15) • *Drop-out Analyses:* Intent to treat - (Repeated ANCOVAs)	• DVP + quetiapine (n = 15) – mean quetiapine dose = 432 mg/day • Provided for 6 weeks	• 53% of quetiapine and 93% of placebo group completed intervention • Significantly greater clinical response in DVP + quetiapine group (87%) vs. DVP + placebo group (53%) • No group differences in positive symptoms, depression, overall functioning, or as-needed lorazepam use • Significantly greater sedation in the quetiapine DVP + group
Emsley[37] (International)	• n = 183 • *Age:* 15-50 years • *Sex:* 71% male • *Ethnic Majority:* Caucasian (62%) • *Diagnosis:* Schizophrenifor m disorder (93%) • *Other Information:* First episode	• *Comparison Group(s):* Haloperidol – dose range = 2-16 mg/day; mean = 5.6 mg/day • *Drop-out Analyses:* Intent to treat	• Risperidone – dose range = 2-16 mg/day; mean = 6.1 mg/day • Provided for 6 weeks	• 80% of risperidone and 69% of haloperidol group completed intervention • 63% of risperidone and 56% of haloperidol group met response criteria: - at < 6mg/day, 74% of risperidone and 62% of haloperidol group met response criteria - at > 6 mg/day, 59% of risperidone and 55% of haloperidol group met response criteria • Overall, significant decrease in symptoms (no group differences) • Haloperidol group experienced significantly more extrapyramidal side effects and received significantly more anticholinergics • Post-hoc analyses revealed dose-related side effects in both groups (better responses for low doses)

TABLE 4. Pharmacotherapy for Early Psychosis, continued

Study	Sample	Design	Intervention	Findings
Geller, Cooper, Sun et al.[28] (US)	• n = 24 • *Age:* 12-18 years • *Sex:* 64% male • *Ethnic Majority:* Caucasian (100%) • *Diagnosis:* Bipolar disorder with substance dependence	• *Comparison Group(s):* Placebo (n = 12) • *Drop-out Analyses:* Intent to treat -completers	• Lithium (n = 13) – 0.9 – 1.3 mEq/L serum levels • Provided for 6 weeks	• 77% of lithium and 92% of placebo group completed intervention • 46% of lithium and 8% of placebo group met response criteria • Significantly fewer positive urine drug screens in lithium group (i.e., decreased drug use) • No significant group differences in mood • More polydipsia and polyuria in lithium group
Kane, Rifkin, Quitkin et al.[26] (US)	• n = 28 • *Age:* mean = 22 years • *Sex:* 50% male • *Ethnic Majority:* Not reported • *Diagnosis:* Schizophrenia (100%) • *Other Information:* First episode	• *Comparison Group(s):* Placebo (n = 17) • *Drop-out Analyses:* Not reported	• Fluphenazine (n = 11) – dose range = 5-20 mg/day oral or 12.5-50 IM every two weeks • Provided for 1 year	• 45% of fluphenazine and 59% of placebo group completed intervention • 0% of fluphenzine and 41% of placebo group relapsed • 42-month follow-up: - 93% of original sample assessed - medication compliance unknown • Overall, 69% experienced a second episode either during drug trial or during follow-up, and of those, 77% experienced a third episode
Lane, Chang, Chiu et al.[63] (Taiwan)	• n = 24 • *Age:* 18-45 years • *Sex:* 65% male • *Ethnic Majority:* Chinese (100%) • *Diagnosis:* Schizophrenia (100%) • *Other Information:* All drug-naïve, first episode	• *Comparison Group(s):* High dose risperidone (n = 12) – 6 mg/day • *Drop-out Analyses:* Intent to treat (LOCF)	• Low dose risperidone (n = 12) – 3 mg/day • Provided for 6 weeks	• 83% of sample completed intervention • 64% of low dose and 67% of high dose group met response criteria • Lower side effect ratings and fewer anticholinergic meds required in low dose group • No group differences in time to response (median = 28 days)

TABLE 4. Pharmacotherapy for Early Psychosis, continued

Study	Sample	Design	Intervention	Findings
Lieberman, Phillips, Stroup et al.[60] (China)	• n = 164 • *Age:* 15-42 years • *Sex:* 52% male • *Ethnic Majority:* Chinese (100%) • *Diagnosis:* Schizophrenia (100%) • *Other Information:* All treatment naïve, first episode	• *Comparison Group(s):* Chlorpromazine (CPZ; n = 83) – median dose = 400 mg/day • *Drop-out Analyses:* Intent to treat (LOCF)	• Clozapine (n = 81) – median dose = 300 mg/day • Provided for 52 weeks	• 85% of clozapine group and • 78% of CPZ group completed intervention • 81% of clozapine and 79% of CPZ groups met response criteria • Significantly faster time to remission in clozapine group • No group differences in psychiatric symptoms, rehospitalization rates, extrapyramidal side effects, or glucose metabolism • CPZ group demonstrated more blurred vision, sweating, dry mouth, akathisia, higher heart rate and longer QT intervals • All CPZ patients were on prophylactic anticholinergic medication • In both groups, longer DUP associated with lower chance of achieving remission • 135-week follow-up: Trend towards greater % weight gain for clozapine vs. CPZ group (9.9 kg vs. 6.5 kg)

TABLE 4. Pharmacotherapy for Early Psychosis, continued

Study	Sample	Design	Intervention	Findings
Lieberman, Tollefson, Tohen et al.[61] (US & Europe)	• n = 263 • *Age:* 16-40 years • *Sex:* 82% male • *Ethnic Majority:* Caucasian (53%) and Black (38%) • *Diagnosis:* Non-affective psychoses • *Other Information:* First episode	• Parallel groups design • *Comparison Group(s):* Haloperidol – mean dose = 4.4 mg/day • *Drop-out Analyses:* Intent to treat (LOCF and random regression coefficients analyses)	• Olanzapine – mean dose = 9.1 mg/day • Provided for 12 weeks during acute phase	• 68% of olanzapine and 54% of haloperidol group completed intervention • 55% of olanzapine and 46% of haloperidol group met response criteria • Using LOCF analyses, there was a significant decrease in positive/negative symptoms and depression in both groups, but no group differences • Using regression analyses, there was a significantly greater decrease in positive/negative symptoms and depression in the olanzapine group • Haloperidol group showed significantly more extrapyramidal side effects and received significantly more anticholinergics, propranolol, and benzodiazepines • 62% of olanzapine group gained more than 7% of body weight (vs. 23% of haloperidol group)
Merlo, Hofer, Gekle et al.[36] (Switzerland)	• n = 52 • *Age:* 16-40 years • *Sex:* 55% male • *Ethnic Majority:* Not reported • *Diagnosis:* Non-affective psychoses • *Other Information:* First episode	• Parallel groups design – matched on neuropsychology motor tests • *Comparison Group(s):* High dose risperidone (4mg/day) • *Drop-out Analyses:* Intent to treat	• Low dose risperidone (2 mg/day) • Provided for 8 weeks	• 87% of low dose and 73% of high dose group completed intervention • Overall, significant decrease in psychiatric symptoms • No group differences in symptoms or functioning • Symptomatic remission criteria met at 8 weeks for 70% low dose and 77% for higher dose • 2 low dose and 3 higher dose patients received biperiden for dystonia • No patient withdrawals due to side effects • Motor functioning significantly better in low dose group

TABLE 4. Pharmacotherapy for Early Psychosis, continued

Study	Sample	Design	Intervention	Findings
Sanger, Lieberman, Tohen et al.[59] (International)	• n = 83 • *Age:* mean = 28.4 years • *Sex:* 71% male • *Ethnic Majority:* Caucasian (84%) • *Diagnosis:* Non-affective psychoses • *Other Information:* Early psychosis (within 5 years of first episode)	• *Comparison Group(s):* Haloperidol (n = 24) – mean dose = 10.8 mg/day • *Drop-out Analyses:* Intent to treat	• Olanzapine (n = 59) – mean dose = 11.6 mg/day • Provided for 6 weeks	• 73% of olanzapine and 38% of haloperidol group completed intervention • Significantly higher clinical response in olanzapine group (67% vs. 29% in haloperidol group) • Significantly greater decrease in positive and negative symptoms in the olanzapine group • Haloperidol group experienced significantly more extrapyramidal side effects and received significantly more anticholinergic medications • Greater % weight gain for olanzapine (4.1 kg) vs. haloperidol group (0.5 kg)
Scottish research group[62] (UK)	• n = 46 • *Age:* 16-68 years (mean = 30) • *Sex:* 46% male • *Ethnic Majority:* Not reported • *Diagnosis:* Schizophrenia (100%) • *Other Information:* First episode	• *Drop-out Analyses:* Listwise	• Flupenthixol (n = 23; mean dose = 20 mg) vs. pimozide (n 23; mean dose = 18.8 mg) • Provided for up to 5 weeks	• 78% of pimozide and 87% of flupenthixol group completed intervention • 63% of sample met response criteria (no group differences) • Both drugs led to significant improvements in functioning and symptoms (no group differences) • No significant group difference in parkinsonism

TABLE 4. Pharmacotherapy for Early Psychosis, continued

Study	Sample	Design	Intervention	Findings
Sikich, Hamer, Bashford et al.[27] (US)	• n = 50 • *Age:* 8-19 years (mean = 15) • *Sex:* 60% male • *Ethnic Majority:* Caucasian (60%) • *Diagnosis:* Mixed affective and nonaffective psychoses • *Other Information:* 78% first episode	• *Comparison Group(s):* Haloperidol – mean dose = 5 mg/day • *Drop-out Analyses:* Intent to treat (LOCF)	• Olanzapine or risperidone: 1) Olanzapine – mean dose = 12.3 mg/day 2) Risperidone – mean dose = 4.0 mg/day • Provided for 8 weeks	• 87% of olanzapine, 53% of risperidone and 53% of haloperidol group completed intervention • 88% of olanzapine, 74% of risperidone and 53% of haloperidol group met response criteria • Haloperidol group demonstrated the slowest rate of response • Significant reductions in symptoms for all groups (no group differences) • Differential average weight gain across groups (7.1 kg for olanzapine; 4.9 kg for risperidone; and 3.5 kg for haloperidol) • Motor side effects common to all drugs; anticholinergics used to treat EPS in > 50% of each group • Similar prolactin-related effects across groups

4 PSYCHOSOCIAL INTERVENTIONS

The provision of psychosocial interventions is considered vital to early intervention. The review contains separate tables for CBT and family interventions and a discussion of psychoeducation. Combination therapies are discussed in the review of early psychosis programs. Each study needed to include a control group to be included in a table. Randomized controlled trials were found for CBT and family intervention. Randomization is often very difficult to achieve especially when program effectiveness is being examined.

4.1 Cognitive Behaviour Therapy

Controlled Trials

Three randomized controlled trials with blinding that examined CBT versus standard care were conducted in the UK (see Table 2). Of the three, only the SoCRATES[66,67] trial had a substantial number of subjects. Both the SoCRATES and Haddock[68] studies found few differences favoring CBT over manualized supportive counselling. One study (Drury[69-71]) that used informal support and recreation therapy as a control found better reduction of positive symptoms and quicker remission for CBT. However, only 70 per cent of subjects were within the first five years of psychosis and data was not analyzed separately for those with more chronic psychoses. Follow-up results indicated CBT was associated with greater perceived self-control over the illness, and both CBT and a formal Supportive Counselling therapy produced lower symptom scores than routine care or informal support.

Two randomized controlled studies addressed suicidality. One study (OPUS[72]) employed an integrated treatment model (see Table 4 on early psychosis programs for details) while the other tested a CBT-based treatment (LifeSPAN[73]). Both trials found that individuals receiving interventions for suicide prevention showed decreased hopelessness (a factor associated with suicide risk). Although the experimental groups did not differ significantly from the controls on measures of suicide attempts, this may reflect the short follow-up periods. The CBT treatment also produced superior quality of life ratings that were maintained at follow-up.

Another CBT study that lacked random assignment found better depression and quality of life scores compared to controls (COPE[74,75]). These differences disappeared at follow-up but the high dropout rates from the control groups obfuscate interpretation. A small study of combined individual and group interventions (Hodel[76]) aimed at increasing coping and decreasing arousal did not produce differences on social or emotional functioning compared to standard care but a trend to better social integration was found at an eight month follow-up.

Conclusions about efficacy of CBT for early psychosis are limited due to the differences in assessed outcomes across studies and the small number of subjects in most studies. However, the overall results for CBT are not without promise, as there appear to be some significant and longer lasting benefits. Further research into CBT for early psychosis is clearly warranted given these findings and in consideration of the more established efficacy of CBT for treatment-resistant schizophrenia (for review see[77]).

At this stage, its clinical use within early psychosis should be limited to individuals demonstrating prolonged recovery or secondary morbidities such as depression as there is a more established CBT literature to provide guidance for these problem areas.

TABLE 5. Cognitive Behaviour Therapy in Early Psychosis

Study	Sample	Design	Intervention	Findings
COPE **Jackson, McGorry, Edwards et al.**[74] **Jackson, McGorry, Henry et al.**[75] **(Australia)**	• n = 80 • *Age:* 16-30 years (mean = 30.7 years) • *Sex:* 64% male • *Ethnic Majority:* Not reported • *Diagnosis:* Mixed affective and nonaffective psychoses • *Other Information:* First episode	• *Random Assignment:* No • *Blinded:* Not reported • *Comparison Group(s):* 1) refusal group – EPPIC outpatient clients (n = 21) 2) control group – received EPPIC inpatient care only (n = 15)	• Manual-based individual CBT (n = 44) focused on: 1) assessment (e.g., explanatory model) 2) engagement 3) coping skills, behavioural activities, and dealing with cognitive 'roadblocks' 4) secondary morbidity treatment • 40-minute sessions provided once every week or 2 weeks (mean total sessions = 18; range = 2-40)	• 100% of sample completed post-treatment assessment • In comparison to control group, COPE participants demonstrated superior understanding of illness (i.e., explanatory models), less depression and superior quality of life • In comparison to refusal group, COPE group demonstrated superior integration • No group differences in hospital readmissions • 1-year follow-up: - 64% of sample assessed - in comparison to refusal group, COPE participants less likely to seal-over - no significant differences on other psychological/ symptom measures or hospital readmissions

TABLE 5. Cognitive Behaviour Therapy in Early Psychosis, continued

Study	Sample	Design	Intervention	Findings
Drury, Birchwood, Cochrane et al.[69,70] **Drury, Birchwood & Cochrane**[71] **(UK)**	• n = 40 • *Age:* 19-55 years (mean = 30.7 years) • *Sex:* 63% male • *Ethnic Majority:* Caucasian (60%) • *Diagnosis:* Nonaffective psychoses • *Other Information:* 70% within first 5 years of illness	• *Random Assignment:* Yes • *Blinded:* No (outcome raters neither blind nor independent) • *Comparison Group(s):* Recreation therapy and informal support (n = 20)	• Cognitive Therapy group (CT; n = 20) received: 1) individual CT 2) group CT 3) family engagement 4) structured activity program • Provided for 12 weeks (8 hrs/week)	• Both groups demonstrated marked reduction in positive symptoms over 12 weeks, but significantly greater decline in CT group from week 7 to week 12 • CT group displayed greater decline in delusional conviction • 6-month follow-up: CT had a significantly greater reduction in recovery time • 9-month follow-up: - 93% of sample assessed - CT group demonstrated fewer positive symptoms and less delusional conviction • 5-year follow-up: - 85% of sample assessed - no differences in relapse rates, positive symptoms or insight - CT group displayed greater perceived "control over illness" - for those with a maximum of one relapse, delusional beliefs and hallucinations were less with CT

TABLE 5. Cognitive Behaviour Therapy in Early Psychosis, continued

Study	Sample	Design	Intervention	Findings
Haddock, Tarrier, Morrison et al.[68] (UK)	• n = 21 • *Age:* mean = 29.1 years • *Sex:* 90% male • *Ethnic Majority:* Caucasian (95%) • *Diagnosis:* Schizophrenia or schizoaffective disorder • *Other Information:* First treatment within 5 years	• *Random Assignment:* Yes • *Blinded:* Outcome rater blind • *Comparison Group(s):* Manual-based supportive counselling and psychoeducation treatment (n = 11)	• Manual-based individual CBT (n = 10) • Provided for 5 weeks (mean total sessions = 10.2) • Booster sessions provided at 1, 2, 3 and 4 months after discharge (mean attended = 1.7)	• 90% of sample completed intervention • Both groups showed significant reductions in severity of psychiatric symptoms but there were no group differences • No group differences in days spent in hospital 2-year follow-up: - 100% of sample assessed (based on case notes) - no significant group differences - within CBT group, trends towards fewer patients relapsing, fewer number of relapses, greater time to recurrence of positive symptoms, and shorter time to hospital readmission
Hodel, Brenner, Merlo et al.[76] (Australia)	• n = 19 • *Age:* 19-42 years (mean = 27.5) • *Sex:* 37% male • *Ethnic Majority:* Not reported • *Diagnosis:* Not reported • *Other Information:* early psychosis; all inpatients	• *Random Assignment:* No • *Blinded:* Not reported • *Comparison Group(s):* Standard rehabilitation + medication (n = 9; matched by age and education)	• Emotion management therapy (EMT) combined with standard rehabilitation and medication (n = 10) • EMT involved individual sessions (focused on relaxation and distraction techniques) and small groups (focused on development of coping strategies) • Provided for 3 – 4 weeks (11 sessions)	• 100% completed intervention • EMT patients improved more than comparison group on measures of cognitive functioning but not emotional well-being or social functioning • Post-hoc analyses revealed that chronic patients improved more than patients with early psychosis • 8-month follow-up: - 100% of sample assessed - trend towards improved social integration in EMT group - 4 of 10 EMT patients relapsed vs. 6 of 9 patients in comparison group

TABLE 5. Cognitive Behaviour Therapy in Early Psychosis, continued

Study	Sample	Design	Intervention	Findings
LifeSPAN **Power, Bell, Mills et al.**[73] **(Australia)**	• n = 56 • *Age:* Not reported • *Sex:* Not reported • *Ethnic Majority:* Not reported • *Diagnosis:* Not reported • *Other Information:* Early psychosis; < 1 year treatment at EPPIC; all highrisk for suicide	• *Random Assignment:* Yes • *Blinded:* Outcome raters blind • *Comparison Group(s):* EPPIC outpatient care (n = 25)	• LifeSPAN therapy plus EPPIC outpatient care (n = 31) • Based on cognitive therapy for suicide prevention • 4 stages: 1) engagement 2) suicide risk assessment 3) cognitive modules 4) final closure • Provided for 10 weeks (8-10 sessions total)	• 70% completed intervention (only 58% of LifeSPAN group) • Both groups improved on measures of suicidal ideation, number of suicide attempts, and psychopathology (no group differences) • LifeSPAN group demonstrated significantly greater improvement in hopelessness and quality of life • 6-month follow-up: - 98% of those completing intervention assessed - both groups further improved on suicidal ideation, number of suicide attempts, and severity of psychiatric symptoms (no group differences) - LifeSPAN group maintained significantly greater improvements in hopelessness and quality of life - one individual from each group committed suicide several weeks before the end of followup

TABLE 5. Cognitive Behaviour Therapy in Early Psychosis, continued

Study	Sample	Design	Intervention	Findings
SoCRATES **Lewis, Tarrier, Haddock et al.**[66] **Tarrier, Lewis, Haddock et al.**[67] **(UK)**	• n = 309 • *Age:* median = 27.4 years • *Sex:* 70% male • *Ethnic Majority:* Caucasian (85%) • *Diagnosis:* Nonaffective psychoses • *Other Information:* First or second admission	• *Random Assignment:* Yes • *Blinded:* Outcome raters blind • *Comparison Group(s):* 1) Manual-based Supportive Counselling (SC; n = 106) 2) Routine Care (RC; n = 102)	• Manual-based individual CBT (n = 101) • Provided for 5 weeks with booster sessions at 2 weeks, 1, 2 and 3 months post-treatment	• 82% of sample completed one or more post-baseline assessments (total = 5) • Significant decreases in symptoms for all groups over first 7 weeks • Non-significant trend for CBT group to improve fastest • No group differences in psychopathology at final post-baseline assessment • 18-month follow-up: - 73% of original sample assessed - CBT and SC groups demonstrated less severe psychopathology than RT group - no differences in relapse/rehospitalization rates, medication dose or compliance

4.2 Family Intervention

Initial results from family intervention studies are encouraging. Three out of four randomized controlled trials included in Table 3 demonstrated positive effects of family involvement. In comparison to standard outpatient care, benefits included reduced relapse rates (Goldstein;[78] Zhang[79]) and less residual psychopathology (Goldstein;[78] De Giacomo[80]). Similarly, two non-randomized controlled trials demonstrated fewer relapses (Rund[81]) and less inpatient and outpatient treatment among early psychosis patients whose families received intervention (Lehtinen[82]). However, the advantage of family therapies over more specialized psychosocial treatment programs is less apparent. The fourth randomized controlled trial found that the addition of family intervention to patient-oriented psychotherapy did not reduce patient relapses (Linszen[83-85]). This result may have been due to the low overall relapse rate (16 per cent over one year) and reflect the efficacy of the psychosocial interventions given to the control group.

Although preliminary results are encouraging, there has been little consistency in the family interventions applied across studies. Some focus primarily on psychoeducation, while others involve system- or crisis-oriented approaches. Overall, limited attempts to isolate the efficacious components of family interventions in early psychosis have been made. For individuals with long-standing schizophrenia, there is fairly good evidence supporting family interventions designed to decrease expressed emotion (i.e., communication training), decrease relapse rates and improve medication compliance.[86] There is less evidence to suggest, however, that attempts to decrease expressed emotion may be of benefit to patients with early psychosis. Among the studies reviewed, only one (Linszen[83-85]) emphasized communication training. The authors found no effect of their intervention on expressed emotion levels and concluded that explicit attempts to modify communication patterns at the early stages of illness may not be helpful. In fact, it appears that expressed emotion is not a stable index in first-episode families.[87] It has been suggested that early family interventions may best be targeted to prevent the entrenchment of expressed emotion by focusing on appraisals of loss and associated grief reactions.[83,87] Further research is warranted to determine whether family interventions targeting communication training is indicated in early psychosis.

Regardless of the therapeutic approach employed, initial results suggest that the addition of family intervention to standard care is beneficial. This conclusion is further supported by evidence from the schizophrenia literature, where greater evidence for both family psychoeducation[88] and communication training[86] has been obtained. Future research should continue to clarify the unique needs and experiences of families of clients with early psychosis.

TABLE 6. Family Intervention in Early Psychosis

Study	Sample	Design	Intervention	Findings
De Giacomo, Pierri, Santoni Rugiu et al.[80] (Italy)	• n = 38 • *Age:* Not reported • *Sex:* Not reported • *Ethnic Majority*: Not reported • *Diagnosis:* Schizophrenia • *Other Information:* Duration of illness < 3 years	• *Random Assignment:* Yes • *Blinded:* Outcome raters blind • *Comparison Group(s):* Standard pharma-cological treatment group (n = 19)	• Combined pharmacological and family therapy group (n = 19) • Individual family therapy used a paradoxical approach (based on the Elementary Pragmatic Model) • Family sessions provided for 10 weeks (1 session/week)	• 1-year follow-up: - 86% of sample assessed - patients in family therapy group showed significant improvements in symptoms and social activity - 4 cases in family therapy group (vs. none of the families in comparison group) changed from high to low EE
Goldstein, Rodnick, Evans et al.[78] (US)	• n = 104 • *Age:* mean = 23.4 years • *Sex:* 55% male • *Ethnic Majority*: Caucasian (79%) • *Diagnosis:* Schizophrenia • *Other Information:* First or second admission	• *Random Assignment:* Yes • *Blinded:* Outcome raters blind • *Comparison Group(s):* 1) standard outpatient care + highdose fluphenazine (n = 28) 2) standard outpatient care + lowdose fluphenazine (n = 24)	• 2 intervention groups: 1) family therapy + high-dose fluphenazine (n = 25) 2) family therapy + low-dose fluphenazine (n = 27) • Crisis-oriented family therapy focused on acceptance of psychosis, identification of stressors, and future planning • Provided for 6 weeks (1 session/week)	• 92% completed intervention • Least number of relapses in highdose/family therapy group and the highest number in low-dose/no therapy group • Less residual psychopathology in family therapy groups

TABLE 6. Family Intervention in Early Psychosis, continued

Study	Sample	Design	Intervention	Findings
Linszen, Dingemans, Van der Does et al.[83] **Nugter, Dingemans, Van der Does et al.**[84] **Lenior, Dingemans, Schene et al.**[85] **(Holland)**	• n = 76 • *Age:* 15-26 years (Mean = 20.6) • *Sex:* 70% male • *Ethnic Majority*: Caucasian (80%) • *Diagnosis:* Nonaffective psychoses • *Other Information:* Recent-onset	• *Random Assignment:* Yes (stratified by EE status) • *Blinded:* Some raters blind • *Comparison Group(s):* Inpatient and individualoriented psychosocial intervention (IPI; n = 39; also included 2 psychoeducation meetings for families)	• Inpatient, individualoriented and family-oriented intervention (IPFI; n = 37) • Family sessions focused on education, training in communication (i.e., EE reduction), and problem-solving skills • 18 sessions provided over 12-month outpatient period (mean family contacts = 17)	• Overall, low relapse rates across both treatment groups (16%) • Addition of family intervention did not reduce relapse rates • Patients from low EE families receiving family intervention had slightly higher relapse rates • Follow-ups (17-55 months and 6-10 years post-discharge): - no effect of family intervention on EE levels over time - no effect of family intervention on months of psychotic episodes - in both groups, EE was unstable over the years: levels decreased during the first 34 months after intervention, but then increased in subsequent years
Rund, Moe, Sollien et al.[81] **(Norway)**	• n = 24 • *Age:* 13-18 years (Mean = 16.0) • *Sex:* 67% male • *Ethnic Majority*: Not provided • *Diagnosis:* Schizophrenia (96%) and schizoaffective disorder (4%) • *Other Information:* Adolescent-onset	• *Random Assignment:* No • *Blinded:* No • *Comparison Group(s):* Historical control group (n12) - patients treated at same hospital at earlier point in time received standard inpatient/outpatient care	• Family intervention group (n = 12) • Individual family sessions focused primarily on problem-solving • Additional parent seminars (psychoeducational focus) • Provided over 2-year period (initially occur twice/month and eventually are held once every two months)	• 100% completed intervention • Significantly fewer patients with 2 or more relapses in family group • Family intervention program was less expensive

TABLE 6. Family Intervention in Early Psychosis, continued

Study	Sample	Design	Intervention	Findings
Turku Project **Lehtinen[82] (Finland)**	• n = 81 • *Age:* mean = 27.0 years • *Sex:* 50% male • *Ethnic Majority:* Not reported • *Diagnosis:* Nonaffective psychoses • *Other Information:* First-contact	• *Random Assignment:* No • *Blinded:* No • *Comparison Group(s):* Historical control group (n = 53; patients treated in same catchment area 7 years earlier)	• Family intervention group (n = 28) • Involved immediate crisis- and systemoriented family therapy that emphasized changes in interaction system of patient • Variable duration and number of sessions provided (intervals ranged from a few days to 2 months)	• 1-year follow-up: No significant difference in rehospitalization rates between groups • 2-year to 5-year followups: - proportion of patients hospitalized declined significantly in family intervention group - patients in family therapy group used less hospital days and less outpatient treatment - significantly fewer patients in family treatment group went on disability pension
Zhang, Wang, Li et al.[79] (China)	• n = 83 • *Age:* mean = 23.8 years • *Sex:* 100% male • *Ethnic Majority:* Chinese (100%) • *Diagnosis:* Schizophrenia • *Other Information:* First episode	• *Random Assignment:* Yes • *Blinded:* Outcome raters blind • *Comparison Group(s):* Standard outpatient care (n = 41)	• Family intervention group (n = 42) • Included both group and individual family counselling sessions • Sessions focused on attitudes about illness, psychoeducation, and stress management • Provided over 18-month period • Variable number of sessions (mean 6)	• 94% completed intervention • Significantly lower rate of hospital readmission in family intervention group • Significantly longer hospital-free period in intervention group (for those re-admitted) • Within intervention group, patients not readmitted to hospital displayed significantly less psychopathology and higher overall functioning • Overall good medication compliance (no group differences) • Strong additive effect of consistent medication use

4.3 Psychoeducation

Controlled Trials

While much has been written about education for early psychosis, there are few controlled trials on either patient or family education in this area. Stress management is often included as a part of psychoeducation and the effects of stress management alone have not been well researched.

Early psychosis patients who rely more on problem-focused coping strategies reported that they are better able to cope with stress. The use of these strategies is also associated with fewer symptoms and increases in self-efficacy and perceived social support.[89] The one randomized controlled trial investigating the effects of emotional management therapy in early psychosis found cognitive benefits, a trend toward social benefits and lower relapse rates, but no benefits on emotional well-being (see Hodel[76] in Table 2). Stress management has also been shown to reduce relapses in randomized controlled trials for individuals with schizophrenia.[90]

Other Evidence

The number of studies on psychoeducation is much greater for patients with long-standing psychotic disorders. There are clear benefits on relapse rates, compliance and well-being (for reviews see[91,92]). These findings indicate that psychoeducation provides substantial benefits and should be provided to all early psychosis patients and their families.

5 EARLY PSYCHOSIS PROGRAMS

Early psychosis programs are typically multidisciplinary teams that provide a number of services including public education, comprehensive rapid assessment, clinical case management and group interventions. Specific interventions generally include pharmacotherapy, psychoeducation, stress management, relapse prevention, problem-solving, supportive counselling, rehabilitation and social work functions. Specialized services such as family therapy and CBT may also be available. Programs usually strive to provide a complete "package" to clients and their families. This makes evaluation of the entire service dependent upon the availability of suitable existing control groups that may be current or historical.

Controlled Trials

Eight controlled studies representing six programs are included in Table 4. In most studies, specialized early psychosis programs were associated with lower use of antipsychotic medication, lower doses and reduced use of hospitals. The TIPS studies,[93,94] which emphasize early detection, demonstrated reductions in duration of untreated psychosis, better functional outcomes and lower levels of psychopathology that were maintained at follow-up. The COAST study[95] failed to show additional benefits compared to treatment as usual but did find trends to better quality of life and lesser hospital utilization in the specialty service. This study appeared to possess low statistical power. The OPUS study[72] reported lower hopelessness but no differences versus controls on other measures of suicidality.

Another study (API[96]) compared two sets of three treatment sites each with one set providing treatment as usual and the other set delaying use of antipsychotics for several weeks and then continuing to delay if a person continued to improve. The delayed treatment sites employed significantly more family therapy. At two years, only 57 per cent of the delayed medication/family therapy group had received antipsychotics (and at much lower doses) versus 94 per cent of the regular treatment group. The experimental group also showed better outcomes on measures of symptoms, remission and time spent in hospital.

Other Evidence

General client outcomes

One year assessments were performed on 180 out of 257 patients who had entered the Calgary Early Psychosis program.[97] Assessments were performed at baseline, three, six and 12 months. Positive symptoms improved significantly by three months, depression increased by three months but significantly improved by 12 months and negative symptoms changed little over the first year. At one year, 72 per cent were considered to be in stable remission, 20 per cent were in unstable remission, and eight per cent were continuously psychotic. These numbers compare closely with results from another Canadian Program (PEPP).[98] PEPP also reported that after one-year of treatment, early psychosis patients demonstrated significant improvements in self-report assessment of quality of life independent of improvements in symptoms.

Substance abuse

The Calgary Early Psychosis Program had 37 per cent of new admissions meet DSM-IV[99] criteria for a diagnosis of substance abuse or dependence.[100] Substance abuse is addressed in treatment through several intervention strategies within the range of psychosocial interventions provided by the case manager as well as through group interventions. One-year outcome data revealed that the use of hallucinogens and cannabis (but not alcohol) decreased significantly as indicated by case manager ratings.

Suicide

The controlled trials examining suicide were discussed above. In a cohort study of 238 patients in an early psychosis program, 15 per cent had attempted suicide prior to entry into the program.[101] One-year into the program, only 2.9 per cent had made a suicide attempt and 0.4 per cent completed suicide. These rates are lower than other published rates for early psychosis patients. Overall, the reduction in hopelessness found in the randomized controlled trials is promising especially when combined with these low numbers of suicide attempts within an early psychosis program. Suicide prevention is indicated in all individuals with early psychosis assessed to be at risk.

Cost effectiveness

Fifty-one subjects recruited to the EPPIC sample were individually matched with 51 subjects from the pre-EPPIC sample over a one year follow-up period.[102] Data was collected on both outpatient and inpatient resource utilization and associated costs. Only direct costs were included. The results indicated that EPPIC was more cost-effective than pre-EPPIC. The savings were due to a marked reduction in inpatient costs that outweighed the increases in the costs of outpatient care provided through EPPIC.

TABLE 7. Programs for Early Psychosis

Study	Sample	Design	Intervention	Findings
API **Lehtinen, Aaltonen, Koffert et al.** [96] **(Finland)**	• n = 135 • *Age:* 15-44 years (mean = 28.7) • *Sex:* 59% male • *Ethnic Majority:* Not reported • *Diagnosis:* Nonaffective psychoses only • *Other Information:* irst-episode of psychosis	• *Random Assignment:* No • *Blinded:* No • *Comparison Group(s):* Treatment as usual (TAU; n = 51) - antipsychotic medication + some psychological intervention in 53% of patients	• Intensive psychosocial treatment group (n = 84) • Psychotherapeutic and family centered approach • Family therapy was mainly systemicanalytic • Minimal neuroleptic use (when possible, not started, postponed, or avoided entirely)	• 2-year follow-up: - 79% of sample assessed - 57% of experimental group received neuroleptic treatment at some point vs. 94% of the TAU group - significantly lower neuroleptic dosages used in experimental group - overall, favourable outcome for both groups, but experimental group had less hospital treatment, less frequent psychotic symptoms, and higher overall functioning
COAST **Kuipers, Holloway, Rabe-Hesketh et al.**[95] **(UK)**	• n = 59 • *Age:* 18-65 years • *Sex:* 76% male • *Ethnic Majority:* Not reported • *Diagnosis:* Mixed affective and nonaffective psychoses • *Other Information:* irst contact within previous 5 years	• *Random Assignment:* Yes • *Blinded:* Main outcome rater blind • *Comparison Group(s):* TAU; n = 27)	• COAST (n = 32) • Range of interventions offered to clients as needed (not via protocol): - optimum atypical medication - psychological interventions (individual CBT; family interventions) - vocational and welfare help	• 6-, 9-month follow-up: - 72% of sample assessed at either 6 or 9 months (or both) - overall, both COAST and TAU groups improved on measures of global functioning, symptoms, and quality of life (no significant group differences) - trend towards less hospital days for COAST group - trend towards greater increase in carer quality of life in COAST group

TABLE 7. Programs for Early Psychosis, continued

Study	Sample	Design	Intervention	Findings
EPPIC **McGorry, Edwards, Mihalopoulos et al.[103] (Australia)**	• n = 102 • *Age:* 16-30 years (mean = 22.2) • *Sex:* 65% male • *Ethnic Majority:* Not reported • *Diagnosis:* Mixed affective and nonaffective psychoses • *Other Information:* First episode or within first three years of onset of illness	• *Random Assignment:* No • *Blinded:* No • *Comparison Group(s):* Historical control group (n = 51) – matched pre-EPPIC sample that participated in a hospitalbased recovery program	• EPPIC community-based program (n = 51) • Intensive, phasespecific treatment consisting of: - mobile assessment team - inpatient unit - outpatient case management system - day and group program - multi-family group interventions - cognitively oriented psychotherapy (COPE)	• 3-, 6-month and 1-year follow-ups: - 70% of sample assessed - over year, EPPIC sample had significantly fewer admissions and inpatient bed days than pre-EPPIC sample - overall, good medication adherence (no group differences at 3-, 6-months or 1 year) - no group differences in general psychopathology levels - significantly lower negative symptom levels in EPPIC vs. pre-EPPIC group at 3-, 6-month follow-up only - EPPIC group demonstrated significantly higher levels of functioning at 3-, 6-month and 1-year follow-ups
EPPIC **Yung, Organ & Harris[104] (Australia)**	• n = 229 • *Age:* mean = 22.9 years • *Sex:* 55% male • *Ethnic Majority:* Not reported • *Diagnosis:* Mixed affective and nonaffective psychoses • *Other Information:* First treated episode of psychosis or within first two years of illness	• *Random Assignment:* No • *Blinded:* Not reported • *Comparison Group(s):* EPPIC (n = 167) – published evaluative data from 3 different time periods	• Generic Mental Health (n = 62) • Majority receiving case management, 98% receiving antipsychotic medication, and 69% of families involved in treatment	• Only descriptive statistics provided • Higher percentage of patients in Generic MH group were admitted to hospital (81% vs. 64%) and average length of stays were longer (47 vs. 13 days) • Greater police involvement in the admission process in the Generic MH group (40%) vs. EPPIC (4%) • Longer mean DUPs in Generic MH group (469) vs. EPPIC (191)

TABLE 7. Programs for Early Psychosis, continued

Study	Sample	Design	Intervention	Findings
OPUS **Nordentoft, eppesen, Abel et al.**[72] **(Denmark)**	• n = 304 • *Age:* 18-45 years (mean = 27.0) • *Sex:* 60% male • *Ethnic Majority:* Not reported • *Diagnosis:* Predominantly non-affective psychoses; included schizotypal disorder (11%) • *Other Information:* First-episode of psychosis; all high-risk for suicide	• *Random Assignment:* Yes • *Blinded:* Not reported (interviewer was independent) • *Comparison Group(s):* Standard treatment provided through community mental health teams (n = 148)	• Integrated Psychiatric Treatment group (n = 156) received: - assertive community treatment (ACT) - anti-psychotic medication - psychoeducational family treatment - social skills training (when needed)	• 1-year follow-up: - 75% of original sample assessed - no difference between groups on suicidal ideation, number of suicide attempts, depression or tedium vitae - integrated treatment group demonstrated significantly lower levels of hopelessness

TABLE 7. Programs for Early Psychosis, continued

Study	Sample	Design	Intervention	Findings
Swedish Parachute Project **Cullberg, Levander, Holmqvist et al.[105] (Sweden)**	• n = 391 • *Age:* 18-45 years (mean = 28.9) • *Sex:* 52% male • *Ethnic Majority:* Not reported • *Diagnosis:* Majority nonaffective psychoses • *Other information:* First contact	• *Random Assignment:* No • *Blinded:* Not reported • *Comparison Group(s):* 1) historical control group (n = 74) - provided standard treatment consisting of medication and supportive counselling 2) prospective control group (n = 64) - clinic located in different community providing low dose medication and no specific psychosocial treatments	• Parachute Project (n = 253): - intervention without delay - access to stable specialized treatment team - lowest dose antipsychotic with an attempt to avoid during first 1-2 weeks - access to small homelike overnight care - family support and education - psychotherapy as needed – dynamic approach often supplemented with cognitive methods • Treatment provided over a 5-year period	• Among those with schizophrenia syndromes, fewer patients in Parachute group were prescribed antipsychotics in the first week of treatment (and had lower doses) than in both comparison groups Among those with nonschizophrenia syndromes, more patients in historical group were prescribed antipsychotics during the first week (and had higher doses) than both other groups • 1-year follow-up: - 69% of Parachute sample and 100% of comparison groups assessed among those with schizophrenia syndromes, fewer Parachute patients were on antipsychotic medication compared to both comparison groups - among those with nonschizophrenia syndromes, no group differences in use of antipsychotic medication, but historical group had higher doses - Parachute and prospective groups demonstrated significantly higher functioning than historical group - psychiatric inpatient care was significantly lower in the Parachute vs. prospective group - no significant group differences in psychopathology ratings - satisfaction with care was high in the Parachute group

TABLE 7. Programs for Early Psychosis, continued

Study	Sample	Design	Intervention	Findings
TIPS **Larsen, Aaltonen, Koffert et al.** [93] **(Norway & Denmark)**	• n = 109 • *Age:* mean = 25.4 years • *Sex:* 61% male • *Ethnic Majority:* Not reported • *Diagnosis:* Nonaffective psychoses • *Other information:* First-episode	• *Random Assignment:* No • *Blinded:* No • *Comparison Group(s):* Historical control group (n = 43) – data collected from patients in same area 4 years prior	• Early detection (ED) system (n = 66) • Comprehensive multi-level education and service delivery system designed to reduce DUP • ED teams and educational campaigns about early psychosis targeted to the general population, health professionals, and schools	• Baseline assessment: - median DUP reduced from 26 wks in comparison group to 4.5 wks in the ED group - ED group had significantly better premorbid adjustment scores - no differences in overall functioning - less severe symptom profiles in the ED group - more substance abuse in ED group
TIPS **Melle, Larsen, Haahr et al.** [94] **(Norway & Denmark)**	• n = 109 • *Age:* 18-65 years • *Sex:* 59% male • *Ethnic Majority:* Caucasian (93%) • *Diagnosis:* Nonaffective psychoses • *Other information:* First-episode	• *Random Assignment:* No • *Blinded:* No • *Comparison Group(s):* No-Early Detection (ED) areas (n = 140): two health care sectors relying on traditional detection and referral methods; same assessment and treatment protocols as ED areas	• TIPS ED system used in two health care sectors (n = 141)	• Baseline assessment: - significantly shorter DUPs in ED group - ED group had significantly lower symptom levels and higher overall functioning • 3-month follow-up: ED group had significantly lower negative and general psychopathology symptom levels and higher overall functioning than no-ED group

6 PREVENTION/PRODROMAL INTERVENTION

Early intervention may be defined both as treatment early after psychosis onset and as at tempts to prevent onset in individuals considered at high risk. The prodrome is a term used to denote the period of non-specific increase in psychopathology and deterioration in functioning that precedes the onset of an acute episode. These episodes may include either the initial onset of illness or relapses. In this review, the term prodrome is used to describe onset of illness. The trials examined were both concerned with arresting onset. Discussion of relapse intervention is included in the section on pharmacotherapy.

Controlled Trials

The one randomized controlled trial attempting to prevent the progression to psychosis that has been completed is shown in Table 5 (McGorry[106]). This trial investigated whether a combination of low dose antipsychotic and CBT could decrease the likelihood of psychosis developing in an ultrahigh risk group (i.e., showing deterioration in functioning and either subthreshold psychotic symptoms or a strong family history of psychosis). One year after commencement of the study, it was found that those with good medication adherence were significantly less likely to convert to psychosis. Two other randomized controlled trials are currently underway. One study (PRIME[107-109]) relies solely on the use of antipsychotics to prevent transition and the initial results (see table) show the experimental group having fewer symptoms reflective of psychosis (although weight gain was substantial; about four kilograms compared to half a kilogram for placebo). The other study relies solely on the use of CBT to prevent transition but no data have yet been published that differentiate the experimental and control groups. These initial findings are exciting but need to be interpreted with caution. The numbers of subjects in these studies who are exposed to treatment but never would have converted to psychosis is high (i.e., as seen in the control groups). Despite advances in determining who is at-risk for developing psychosis, the risk of "false positives" remains high (about 60 per cent within one year).[110]

Other Evidence

In 1984, in the two small towns of Buckingham and Winslow (population of 35,000), a comprehensive early detection and intervention program was established.[111] Virtually every resident was registered with one of sixteen family practitioners in the area. Early detection of potential episodes of schizophrenia utilized a two-stage approach – family physicians were trained to recognize possible prodromal symptoms and to immediately refer suspected cases to specialized mental health assessment. Individuals suspected of experiencing a prodrome of schizophrenia were then provided with a range of interventions including education, home-based stress management, and time-limited low-dose medication targeted to specific impairments (including confused thinking and insomnia). Continued care and monitoring were provided for two years following resolution of the "prodromal" state. Case detection rates of schizophrenia were considerably lower than expected based on known incidence rates of schizophrenia.

In conclusion, given the risks of falsely identifying individuals and subjecting them to unnecessary treatment, stress and stigma, it is recommended that interventions be limited clinically to needs-based treatment as dictated by the specific presenting problems. Treatments specific for psychosis (antipsychotic medication, education about psychosis, etc.) should not be initiated until psychosis develops. In time, guided by further research, specific interventions to attempt to prevent psychosis may be possible for clinical use. This time has not come yet in routine clinical settings.

TABLE 8. Programs for Preventing Early Psychosis

Study	Sample	Design	Intervention	Findings
McGorry, Yung, Phillips et al.[106] (Australia)	• n = 59 • *Age:* 14-28 years (mean = 20.0) • *Sex:* 58% male • *Ethnic Majority:* Not reported • *Diagnosis:* Ultrahigh risk • *Other Information:* No previous psychotic or manic episode	• *Random Assignment:* Yes • *Blinded:* Attempted single blind outcome raters) • *Comparison Group(s):* Needs-based interventions NBI; n = 28) – supportive psychotherapy	• Specific preventative interventions (SPI; n = 31) • Included NBI + risperidone (1-2 mg) and modified CBT • SPI provided over 6-month period • Risperidone provided daily; CBT frequency varied according to need (mean = 11.3 sessions)	• 100% completed intervention; however, 55% of SPI group demonstrated partial or poor medication adherence • Significantly fewer participants progressed to first episode in SPI group (3) vs. NBI group (10) 6-month follow-up: - 100% of sample assessed - significant group difference in transition rates was not maintained (3 additional participants from SPI group progressed to first episode) - when analyzed according to medication adherence, among those demonstrating good adherence, only 1 of 14 made transition (which was significantly lower than in NBI group)
PRIME **McGlashan, Zipursky, Perkins et al.[107]** **Miller, Zipursky, Perkins et al.[108]** **Woods, Breier, Zipursky et al.[109] (North America)**	• n = 60 • *Age:* 12-36 years (mean = 17.8) • *Sex:* 65% male • *Ethnic Majority:* Caucasian (67%) • *Diagnosis:* Prodromal syndrome • *Other Information:* No past or current psychotic disorder	• *Random Assignment:* Yes • *Blinded:* Double blind • *Comparison Group(s):* Placebo (n = 29)	• Olanzapine (n = 31) • Provided for one year (5-15 mg; once to three times daily dosing)	• 8-week follow-up: - 68% of sample assessed - Olanzapine group demonstrated significantly less prodromal, positive and negative symptoms - no group differences in extra-pyramidal, depressive or manic symptoms - average weight gain of 9.9 lb in olanzapine group vs. 0.7 lb in placebo group

7 DISCUSSION

Controlled Trials

Although high quality research on many intervention areas pertaining to early psychosis is limited, the literature is rapidly evolving. Numerous randomized controlled treatment studies are underway but were excluded from this review. Currently, the most extensive research supports the use of antipsychotic medications. The atypical antipsychotics are particularly well supported with risperidone and olanzapine having the largest literatures. Pharmacotherapy of first episode affective disorders with psychosis is largely guided by studies of established illness and uncontrolled trials.

Psychosocial therapies are less well researched. Some support was found for CBT and manualized supportive therapy. Family studies produced some noteworthy benefits but the variety of methods used does not allow for detailed definition of optimal interventions. Given the design of some studies, it is difficult to know whether it is simply involving families or a particular treatment modality that produced the benefits. Multi-component interventions embodied in specialized programs appear more effective than less intensive and less structured interventions. The interaction of pharmacotherapy and psychosocial effects has received little attention to date. One interesting finding in need of replication was the API study[96] that found an association between intense family work, good outcomes and decreased use of antipsychotic medication. The paucity of quality research on the effects of psychoeducation was surprising given its central importance in most early intervention approaches. Family interventions specifically targeting Expressed Emotion to lower relapse do not appear to be successful in first episode psychosis.

Other Evidence

Any review with stringent criteria for evaluating efficacy may yield few high quality studies. The resulting lack of evidence supporting some interventions in early psychosis should not be taken as proof that the interventions are ineffective or harmful – especially when there is excellent evidence for their efficacy in the general literature. Nevertheless, it cannot be assumed that the transfer from one literature to another is always valid. For this reason, there is value to studies that come from within the early psychosis literature but do not approach the rigor of randomized controlled trials. There is considerable evidence from the early psychosis literature that a variety of pharmacological and psychosocial interventions merit continued use.

One area that clearly needs further work concerns co-morbid disorders and how interventions must be modified or integrated to optimize treatment success. For example, rates of substance abuse are high in early psychosis[112] and substance use is associated with poorer short-term and long-term outcomes.[113] Although controlled trials of psychosocial interventions specific for substance abuse in early psychosis patients are nonexistent, uncontrolled program data are encouraging.[100] Despite the lack of evidence specific to early psychosis, this issue warrants clinical attention. Taking guidance from the schizophrenia literature, an integrated individualized outpatient approach using motivational and behavioural interventions would have the greatest chance of success.[114,115] As noted in the pharmacotherapy section, the evidence that medications effectively treat substance abuse is limited to one trial in bipolar patients.

8 RECOMMENDATIONS

- Atypical antipsychotic medications are effective for acute psychoses. Antipsychotic doses should be low and titrated slowly. The use of multiple antipsychotic medications is not usually warranted. Clozapine should be reserved for treatment refractory cases.
- Lithium remains the first line mood stabilizer when mania accompanies psychotic symptoms.
- Family involvement/interventions are recommended.
- Cognitive behaviour therapy is advised on the basis of limited support in the first episode literature and considerable support from the general schizophrenia and affective disorder literature.
- Psychoeducation receives substantial support in the general literature yet has been infrequently studied in early psychosis despite being an integral component of most programs. Psychoeducation is recommended for all cases.
- Interventions currently used in treating first episode cases are not recommended for use in suspected onset-prodrome cases. Further research on improving the identification rate must be coupled with rigorous treatment trials.
- Current early psychosis guidelines are consistent with the ethics and theoretical framework of the early intervention paradigm and represent an array of interventions that are often embodied in specialized programs. No evidence to date suggests these programs represent an inferior option compared to more traditional treatment approaches. Despite a lack of statistical power, several studies demonstrated clear advantages to integrated programs over standard care. The individual components of these programs that contribute to good outcomes needs further study.
- More research is needed on specific interventions, on mixed interventions embodied in programs, and on prevention approaches. In particular, studies of the effectiveness of psychoeducation and group versus individual therapies are of high priority and must be done using sufficiently sized samples. Outcomes measured should be multidimensional and include quality of life, cost effectiveness and psychosocial functioning. Comparisons both between the atypicals and relative to mood stabilizers and first generation antipsychotics are needed in both affective and nonaffective psychoses. Studies must move beyond short-term evaluation (e.g., less than one year) to ascertain whether early intervention significantly alters the course of disorders over many years.

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