A Systematic Review of the Effect of Early Interventions for Psychosis on the Usage of Inpatient Services

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Objectives: To review and synthesize the currently available research on whether early intervention for psychosis programs reduce the use of inpatient services. *Methods:* A systematic review was conducted using keywords searches on PubMed, Embase (Ovid), PsycINFO (ProQuest), Scopus, CINAHL (EBSCO), Social Work Abstracts (EBSCO), Social Science Citations Index (Web of Science), Sociological Abstracts (ProQuest), and Child Development & Adolescent Studies (EBSCO). To be included, studies had to be peer-reviewed publications in English, examining early intervention programs using a variant of assertive community treatment, with a control/comparison group, and reporting inpatient service use outcomes. The primary outcome extracted number hospitalized and total *N*. Secondary outcome extracted means and standard deviations. Data were pooled using random effects models. Primary outcome was the occurrence of any hospitalization during treatment. A secondary outcome was the average bed-days used during treatment period. *Results:* Fifteen projects were identified and included in the study. *Results* of meta-analysis supported the occurrence of a positive effect for intervention for both outcome measures (any hospitalization OR: 0.33; 95% CI 0.18–0.63, bed-days usage SMD: −0.38, 95% CI −0.53 to −0.24). There was significant heterogeneity of effect across the studies. This heterogeneity is due to a handful of studies with unusually positive responses. *Conclusion:* These results suggest that early intervention programs are superior to standard of care, with respect to reducing inpatient service usage. Wider use of these programs may prevent the occurrence of admission for patients experiencing the onset of psychotic symptoms.

Key words: psychosis/psychotic disorders/early intervention/health care utilization/treatment outcome

Introduction

Psychotic disorders comprise some of the most debilitating conditions in mental health.[1,2] People who suffer from psychotic disorders have a significantly reduced quality of life and life expectancy.[1,2] They often fail to form strong social bonds, and are frequently incapable of developing vocationally and therefore unable to independently support themselves.[3] They also have increased rates of suicide and substance abuse problems.[2,4] Psychotic disorders tend to emerge during late adolescence and early adulthood.[5,6] This is a critical period when people are developing the skills and social capital that determines whether they ascend the socio-economic ladder.[5] Despite this, young adults have historically received less treatment than expected considering the prevalence of mental illness at that age.[6] In the last few decades early intervention programs for psychosis programs have been developed in to prevent long-term loss of function.[6–10]

Early intervention programs generally engage in some form of Assertive Community Treatment,[11–13] which attempts to aggressively treat patients in the community rather than using inpatient services.[14,15] For early intervention in psychosis programs the goal is to keep patients engaged with treatment and prevent them from further psychotic episodes and hospitalizations.[16] Early intervention programs provide services beyond what a typical outpatient service does.[10] These additional services can include staff specialized in psychosis treatment, family/group/individual counseling sessions, assertive case management, low-dose second generation anti-psychotics, and in-home treatment sessions.[10,12,13,17] Using assertive case management to achieve coordinated treatment and continuity of care for patients is a particularly important

aspect of ACT. This generally involves a smaller caseload and a care coordinator that oversees the progress of an individual, even if they start to receive care in an inpatient unit or by another clinician. This method of treatment should also increase adherence to the treatment, as the case manager monitors the treatment of individuals and maintains contact even if they disengage with the service. The care coordinator also works with friends, family, and other individuals to improve the functioning of the individuals outside of treatment, through the use of group psychotherapy and education programs. For examples of specific implementations of these programs, and how they differ from treatment-as-usual, readers are encouraged to read articles by Bodén et al[18] and Petersen et al.[19]

One of the expected benefits of early psychosis interventions is the prevention of hospitalizations.[16] While there have been multiple studies on early intervention programs, many of these studies have relatively small sample sizes.[8,9,16] Nonsignificance in results may be due to a lack of power.[16,20] Examining data from multiple studies could determine what effect these interventions are having.

We conducted a systematic review and meta-analysis of the literature and examined the effect of these enhanced services on inpatient service use. We included studies on those with a first episode of psychosis, comparing an early intervention for psychosis program to a standard treatment control group, reporting hospitalization outcomes, and using any experimental or quasi-experimental design. We aimed to answer the following question: Do these enhanced services for individuals undergoing their first psychotic episode lead to less hospital use?

Methods

Search Strategy

A systematic search of the literature was performed by 2 professional health sciences librarians across a number of relevant databases. While searches varied in keeping with the options available within each database, a combination of controlled vocabulary and keyword queries were used in most cases. The title, abstract, and subject heading (if applicable) fields were searched in all cases. Most commonly used subject headings included: *schizophrenia*, *psychotic disorders*, *psychosis*, *prodrome*, *onset (disorders)*, *early intervention*, *resource allocation*, *health resources*, *cost and cost analysis*, *outcome assessment*, *treatment outcome*, and *health care utilization*. A series of keyword strategies were created to access literature focusing on the concept of first episode and early intervention, which were not as well represented as subject headings: *early detection*, *early assessment*, and *first episode* (the detailed search strategy is available from the corresponding author on request). The following databases were searched from their earliest date of coverage through August 6, 2013: PubMed, Embase (Ovid), PsycINFO (ProQuest), Scopus, CINAHL (EBSCO), Social Work

Abstracts (EBSCO), Social Science Citations Index (Web of Science), Sociological Abstracts (ProQuest), and Child Development & Adolescent Studies (EBSCO). Studies on early intervention were examined for references to potentially relevant studies. These potentially relevant studies were then read to determine their suitability for inclusion.

Selection Criteria

To be included in the review studies needed to meet 4 criteria. First, studies needed to have utilized an assessment of an early intervention program (based on an ACT framework) targeting those with a first-episode of psychosis. Services of interest involved multi-disciplinary staff, specializing in treatment of first-episode psychosis, which used assertive case management to engage in multi-modal treatments. Assertive case management involves smaller caseloads, and the coordination of treatment overseen by one clinician. It stresses maintaining treatment and reducing patient drop out. Second, studies were required to have a control group. Third, at least one of 2 outcomes, bed-days utilized or any occurrence of hospitalization during follow-up, were required. Lastly, selection was limited to peer-reviewed publications in English. Two authors independently assessed the articles (J.R.R. and D.C.).

Data Extraction

Data were extracted from the text of the included articles. Additional data were sought for 7 studies but were only obtained for one study, Petrakis 2012.[21] These additional data were for bed-days usage. For the hospitalization outcome, the data extracted were individuals with at least one hospitalization and number at-risk over the follow-up period. For bed-days utilization, the data extracted were mean bed-days used and the standard deviation. These outcomes were assessed for the period in which the patients were receiving the intervention.

Risk of Bias Assessment

Bias was assessed using guidelines from the Cochrane group. However, most of the studies did not use random assignment to treatment groups; thus, we were unable to use the RCT-based risk of bias assessment. Therefore, a more general bias assessment was utilized. This assessment examines the occurrence of 5 types of bias defined by the cochrane risk of bias tool[22]; selection, performance, detection, attrition, and reporting biases. RCT studies were assessed based on the Risk of Bias criteria, but reported using the above criteria to maintain consistency between RCT and observational studies. Studies were assigned a rate of "low risk," "high risk," or "unclear risk" for each of these types of bias. Studies were assumed to be at "unclear risk" initially. Studies were categorized as being low or high risk if there were sufficient details to assess the study design. As an example, McGorry 1996

and another study (Harris et al[23]) both drew data from the same intervention program. The outcome in Harris et al. was compared between populations with significant differences in diagnosis, and therefore considered at high risk for selection bias. In comparison, McGorry 1996 used a matched design and was considered to be at lower risk for selection bias.

Statistical Analysis

The primary outcome for this study was the occurrence of hospitalizations. This was analyzed as a dichotomous variable measuring whether individual patients had any hospitalizations and also measured as the mean number of bed-days that individuals experienced. Odds ratio (ORs) for the occurrence of any hospitalization during follow-up were calculated for each of the individual studies, along with 95% confidence intervals (95% CI). A pooled OR was derived using the Mantel–Haenszel method. Standardized mean differences (SMDs) and their 95% CIs were calculated for the bed-days used for each of the studies. The inverse variance method was used to derive a pooled estimate of the SMD. Heterogeneity was assessed using the χ^2 test for heterogeneity statistic. If heterogeneity was found to be a potential issue, then a random effects meta-analysis model was utilized.

Forest plots and funnel plots were produced for the included studies. These plots were assessed for unusual results, or evidence of publication bias. Sensitivity analysis was conducted to determine if removal of potentially biased studies changed the result of the meta-analysis. All analyses were conducted using RevMan version 5.2.[24]

Results

Study Selection

A PRISMA diagram of the search is provided (figure 1). The search identified 4907 records after removing duplicates. A scan of abstracts and titles identified 177 potentially relevant articles. A total of 45 publications presenting relevant data were identified. Due to the occurrence of multiple publications per research program/sample, one study from each program identified was chosen to represent the research. A total of 15 studies were included in the final analysis. Two studies were derived from the EPPIC program in Australia, McGorry 1996 and Harris 2008. These 2 studies used different methods, measured different outcomes, and arrived at different results. McGorry 1996 used a stronger methodology and was considered to be at lower risk of bias. Therefore the results of this study were used, rather than the results of Harris 2008. Otherwise, the study selected to represent any specific program was the earliest study with full data included (ie, the study from which the data for the current meta-analysis was derived). Details for the included studies are located in Table 1 (additional
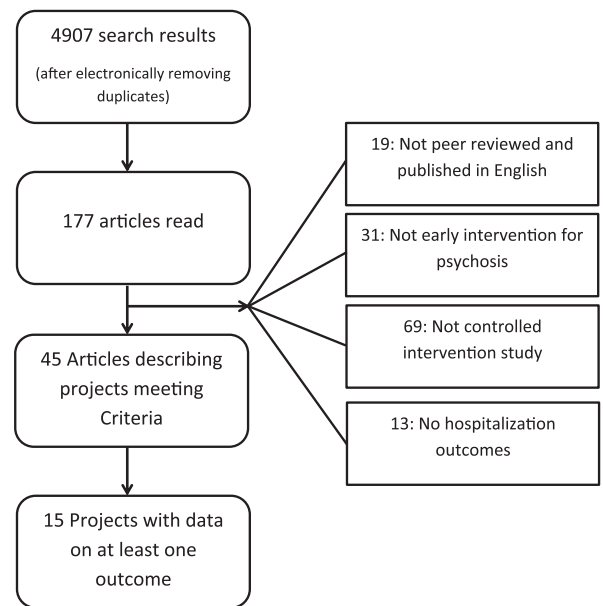

Fig. 1. PRISMA diagram.

details found in supplementary table 1). Most of the studies were conducted in commonwealth countries; the United Kingdom (5),[9,20,25–27] Australia (3),[21,23,28,29] and Canada (1).[30] Scandinavian countries produced 4 of the studies; Sweden (2),[18,31] Denmark (1),[11] and Norway (1).[32] The remaining 2 were in Italy and Hong Kong.[16,33] All but one study included was published after 2000. Most of the studies were observational with only 3 RCT studies included. Two studies utilized matching; McGorry 1996 and Chen 2011. McGorry 1996 matched on gender, age, diagnosis, marital status, and PAS index score at baseline. Chen 2011 matched on gender, diagnosis, and age. Based on the descriptions provided, there appears to be good agreement in treatment modality. However, specifics about the quality and adherence to the treatment plan are insufficient to fully explore the potential for differences in treatment based on the included studies.

Risk of bias

The results of the bias assessment are in supplementary table 2. Most of the studies were free of clear biases. The observational studies generally had unclear risk for selection bias, mainly due to using controls from different times and places. The observational studies frequently found differences in demographic variables, however it is unclear how much these factors will bias the outcome.

In general these studies had low bias in their outcome assessments due to a reliance on administrative records, often collected before the study commenced. Only one study appears to be at risk of attrition bias, Cullberg 2002. This study had a significantly higher rate of attrition in the intervention group with a large enough proportion of

the treatment population missing (31%) that significant bias could have occurred. The remaining studies were considered to be at low risk for attrition and detection biases.

Performance bias, or bias due to the groups being exposed to treatment differences beyond the intervention of interest, is difficult to assess for these studies. The intervention itself is a significant change in performance, and it is unlikely that people in the treatment group received any sort of special benefits that would not be considered part of the intervention. However, there is the possibility that there would remain differences in performance that are due to the use of historical controls or controls from different regions, which most of the observational studies employed. These studies are considered to be at unclear risk.

Due to the outcomes being an inclusion criterion the rate of reporting bias was low in these studies. However, 3 studies did not provide both outcomes of interests, leading to a risk that poor outcomes could have been excluded from these publications.

Individual Analysis

Many of the individual studies failed to find a significant relationship between the intervention and the occurrence of hospitalization. This was true for both the binary hospitalization measure and the mean number of bed days. Out of the 13 studies with the hospitalization outcome, 5 studies found a significant effect for the intervention; Cullberg et al. 2002 (OR: 0.27; 95% CI: 0.15–0.48), Chen 2011 (OR: 0.05; 95% CI: 0.03–0.08), Fowler 2009 (OR: 0.00; 95% CI: 0.00–0.05), McGorry 1996 (OR: 0.05; 95% CI: 0.00–0.89), and Petrakis[21] (OR: 0.31; 95% CI: 0.14–0.71). The remaining 9 studies had nonsignificant results that favoured the intervention.

For the inpatient bed-day outcome, all of the 11 studies favored the intervention group. A total of 6 studies found a significant reduction in the use of inpatient beds. These studies were; Chen 2011 (SMD: −0.42; 95% CI: −0.52 to −0.31), Dodgson 2008 (SMD: −0.36; 95%CI: −0.65 to −0.06), Fowler 2009 (SMD: −1.07; 95% CI: −1.38 to −0.76), Boden 2010 (SMD: −0.35; 95% CI: −0.69 to −0.02), McGorry 1996 (SMD: −0.45; 95% CI: −0.84 to −0.06), and Petrakis[21] (SMD: −0.54; 95% CI: −0.90 to −0.18). The results of the remaining 5 studies were; Bertelson 2008 (SMD: −0.17; 95% CI: −0.34 to 0.00), Goldberg 2006 (SMD: −0.22; 95% CI: −0.44 to 0.01), Craig 2004 (SMD: −0.22; 95% CI: −0.56 to 0.12), Agius 2010 (SMD: −0.17; 95% CI: −0.52 to 0.18), and Cocchi 2011 (SMD: −0.36; 95% CI: −0.94 to 0.23).

Meta-Analysis

Results of the meta-analysis for the hospitalization outcome are presented in figure 2. The meta-analysis found that those who received the early intervention had a significantly reduced risk of being hospitalized at least once during the follow-up period (OR = 0.33; 95% CI: 0.18–0.63; $P = 0.0007$). There was significant heterogeneity amongst the studies ($I^2 = 91\%$; $\chi^2 = 135.90$, $df = 12$; $P < 0.00001$).

Results of the meta-analysis for the bed-days outcome are presented in figure 3. Meta-analysis for the effect of the intervention on inpatient bed-day usage also found a significant reduction (SMD = −0.38; 95% CI= −0.53 to −0.24). Once again, heterogeneity was present among the results of the various studies ($I^2 = 67\%$; $\chi^2 = 30.67$, $df = 10$; $P = 0.0007$).

Sensitivity Analysis

There were several concerns identified that could affect the results of the review, particularly the meta-analysis. Heterogeneity in the studies was one concern. Three studies were responsible for the heterogeneity in the sample; Chen 2011, Cullberg 2002, and Fowler 2009. Chen 2011

Table 1. Summary of Included Studies

Study	Country	Design	Outcomes	Program
Agius 2010	UK	Cohort	Both	
Bertelson 2008	Denmark	RCT	Both	OPUS
Boden 2010	Sweden	Historical control	Both	
Chen 2011	Hong Kong	Matched historical control	Both	EASY
Cocchi 2011	Italy	Cohort	Bed days	Programma 2000
Craig 2004	UK	RCT	Both	LEO
Cullberg 2002	Sweden	Cohort and Historical control	Hospitalization	Parachute
Dodgson 2008	UK	Historical control	Bed days	
Fowler 2009	UK	Historical control	Both	
Goldberg 2006	Canada	Historical control	Both	PEPP
Grawe 2006	Norway	RCT	Hospitalization	
McGorry 1996	Australia	Matched historical control	Both	EPPIC
Petrakis 2012	Australia	Historical control	Both	EPP
Sandbrook 2006	Australia	Historical control	Hospitalization	
Singh 2007	UK	Cohort	Hospitalization	ETHOS

and Cullberg 2002 were only heterogeneous for the hospitalization outcome, whereas Fowler 2009 was heterogeneous for both outcomes. These studies found a positive effect of the intervention which was noticeably larger than the effect of the other included studies. Removing the heterogeneous studies from the analysis did not change the significance of the meta-analysis.

Funnel plots were produced for the 2 outcomes, excluding the nonheterogeneous studies. The funnel plot for the hospitalization outcome (supplementary figure 1) appears to be skewed with more studies than expected favouring the intervention, particularly studies with smaller samples. However the bed-days outcome appears very well balanced in the funnel plot (supplementary figure 2). It is not clear why the hospitalization outcome may suffer from publication bias while the bed-days outcome does not. It is possible the hospitalization outcome is considered more interesting by journals and therefore more at risk of publication bias.

Another concern is the unusually high admission rate in some of the studies, which was close to 100% in one or both of the exposure groups. These studies also tended to be smaller and had large effect sizes. It is unclear why the admission rates were so high in these studies. It is possible that the some other factors could be causing the higher admission rate and larger effect sizes, and also

biasing the results of the meta-analysis. Removing studies where over 50% of the patients had been admitted did not affect the significance of the meta-analysis, though it increased the OR estimate noticeably (OR = 0.74; 0.59–0.93). Removing these studies from the bed days analysis made no appreciable difference (SMD = −0.22; −0.33 to −0.11).

The results from the RCT studies were also analyzed separately. For the bed days outcome the result was significant (SMD = −0.18; −0.33 to −0.03). The hospitalization outcome had a P-value of exactly 0.05 (OR = 0.73; 0.53–1.00).

Discussion

There have been multiple attempts to assess the effectiveness of assertive early interventions for psychosis, most in the last decade. However, these studies have often been significantly underpowered due to small sample sizes. The studies identified in this review favored the intervention, however, just under half of the outcomes measured were significant. Meta-analysis of these results suggested that there may be a significant effect in favor of early intervention. This was true for both reducing time spent in hospital and for preventing the occurrence of any hospitalization.
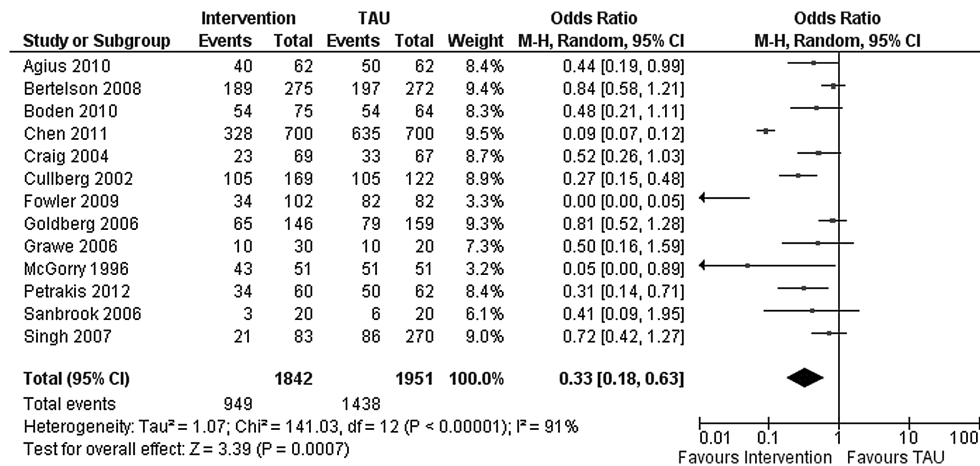
Study or Subgroup	Intervention Events	Total	TAU Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Agius 2010	40	62	50	62	8.4%	0.44 [0.19, 0.99]
Bertelson 2008	189	275	197	272	9.4%	0.84 [0.58, 1.21]
Boden 2010	54	75	54	64	8.3%	0.48 [0.21, 1.11]
Chen 2011	328	700	635	700	9.5%	0.09 [0.07, 0.12]
Craig 2004	23	69	33	67	8.7%	0.52 [0.26, 1.03]
Cullberg 2002	105	169	105	122	8.9%	0.27 [0.15, 0.48]
Fowler 2009	34	102	82	82	3.3%	0.00 [0.00, 0.05]
Goldberg 2006	65	146	79	159	9.3%	0.81 [0.52, 1.28]
Grawe 2006	10	30	10	20	7.3%	0.50 [0.16, 1.59]
McGorry 1996	43	51	51	51	3.2%	0.05 [0.00, 0.89]
Petrakis 2012	34	60	50	62	8.4%	0.31 [0.14, 0.71]
Sanbrook 2006	3	20	6	20	6.1%	0.41 [0.09, 1.95]
Singh 2007	21	83	86	270	9.0%	0.72 [0.42, 1.27]
Total (95% CI)		**1842**		**1951**	**100.0%**	**0.33 [0.18, 0.63]**
Total events	949		1438			

Heterogeneity: Tau² = 1.07; Chi² = 141.03, df = 12 (P < 0.00001); I² = 91%
Test for overall effect: Z = 3.39 (P = 0.0007)

Fig. 2. Meta-analyses for any hospitalization during follow-up period.

Study or Subgroup	Intervention Mean	SD	Total	TAU Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Agius 2010	23.63	47.75	62	30.66	33.74	62	7.9%	-0.17 [-0.52, 0.18]
Bertelson 2008	96	146.7	275	123	170.6	272	12.8%	-0.17 [-0.34, -0.00]
Boden 2010	38	37	75	59	78	64	8.3%	-0.35 [-0.69, -0.02]
Chen 2011	61.6	105.5	700	113.7	141.6	700	14.3%	-0.42 [-0.52, -0.31]
Cocchi 2011	242	408.5	23	542	1,091.1	23	4.3%	-0.36 [-0.94, 0.23]
Craig 2004	35.5	78.9	68	54.9	93.6	66	8.2%	-0.22 [-0.56, 0.12]
Dodgson 2008	44.9	100.3	75	96.7	167.5	114	9.3%	-0.36 [-0.65, -0.06]
Fowler 2009	45.1	113.8	102	165.5	109	82	8.9%	-1.07 [-1.38, -0.76]
Goldberg 2006	43.65	60.9	159	60.18	90.67	146	11.2%	-0.22 [-0.44, 0.01]
McGorry 1996	9.6	20.3	51	25.4	45.1	51	7.1%	-0.45 [-0.84, -0.06]
Petrakis 2012	22.6	24.05	60	46.5	57	62	7.7%	-0.54 [-0.90, -0.18]
Total (95% CI)			**1650**			**1642**	**100.0%**	**-0.38 [-0.53, -0.24]**

Heterogeneity: Tau² = 0.03; Chi² = 30.67, df = 10 (P = 0.0007); I² = 67%
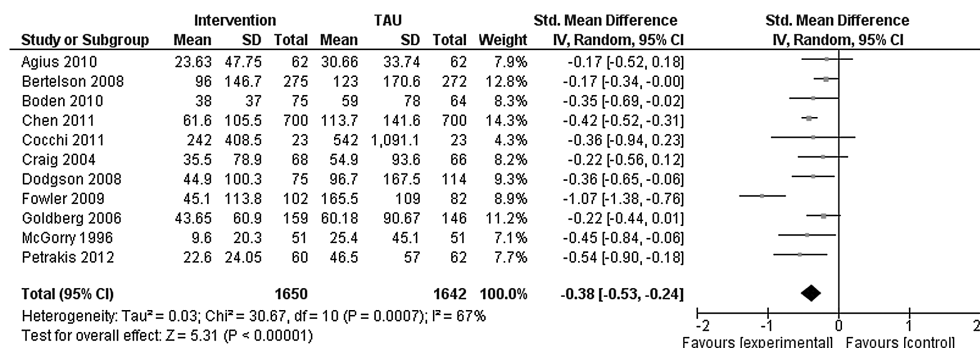Test for overall effect: Z = 5.31 (P < 0.00001)

Fig. 3. Meta-analysis of inpatient bed-days.

This suggests that the failure to find significant results in many of the original studies was due to low power as hypothesized. However, there are some potential areas of concern with respect to the meta-analysis itself. There are potential issues with combining the results of non-randomized studies in meta-analysis.[34,35] It has been suggested that combining these types of studies makes the result of the meta-analysis difficult to interpret.

Assessment of the heterogeneity between studies, and observational studies in particular, is an important part of a meta-analysis.[35] There was significant heterogeneity between the included studies. However, despite the heterogeneity, the results were still consistently positive. The outcome measures used were consistent within studies and should be fairly objective. However, the interventions implementation may vary, and there were differences between countries with respect to the support provided to mental health patients in the comparison groups. There was variation in the frequency in which hospital admissions occurred between the studies. Standardized mean differences were used because of this significant variation. Likewise the length of follow-up varies among the studies, which likely affected the "any hospital admission" variable (over time the probability of admission for both groups would move closer to 1). Sensitivity analysis showed that studies with unusually high admission rates might be increasing the effect size in the meta-analysis. However, the intervention was still significant without including these studies.

Although these interventions appear to have an effect on the use of inpatient services, it is not exactly clear which aspects of the treatment could be responsible. Better use of medication is one possible mechanism. Data on medication use was not available for half of the included studies. Those studies that reported dosage and whether first or second generation antipsychotics were used suggested that these programs may result in lower dosage (though not all studies reported the decrease was significant), and increased use of second generation antipsychotics. However, some of the studies also mentioned that the low-dose treatment method also occurred in their control group. The assertiveness of the programs may have reduced inpatient use by increasing adherence to treatment and continuity of care for patients in the community.[19,25] Perhaps the simplest explanation of this effect is that these services simply increase the availability of treatment in the community and therefore reduce the need to rely on inpatient units for treatment.

Strengths and Limitations

One strength of this review was its broader scope with respect to study design. Although randomized trials are superior in terms of their ability to control unmeasured confounders, non-randomized methods can also provide valuable data with respect to the effectiveness of an intervention in practice. This study assessed the range of research data available and provides a more complete understanding than focusing on what the handful of randomized studies would have provided. Another strength was the relative reliability of the outcome measures. Measuring psychological symptoms is susceptible to measurement errors and rater bias. The cases in this study relied on more discrete and measurable outcomes. Furthermore, research has suggested that hospital admission is a valid outcome measure for the effectiveness of interventions for psychotic disorders.[36]

One limitation of the analysis was the reliance on unadjusted results. The designs of these studies tried to reduce the effect of factors such as selection bias. Some studies utilized matching designs to reduce bias due to gender, diagnosis, and other between group disparities. However, bias appears possible among the other observational studies. However, sensitivity analysis was used to test the effect of removing potentially biasing studies from the meta-analysis and found the results to be robust in favor of a positive effect. Hospital use in the studies appears to be any use of inpatient services, potentially including nonpsychiatric services. This is not a serious limitation since reduction of nonpsychiatric hospital use would also be beneficial for patients. Lastly, the effect of variations in both implementation of the intervention as well as the standard of care among the study cannot be clarified and may introduce some bias. Although the studies appear to adopt the key components of ACT, we are unable to directly assess how well these components are implemented across the various research sites and whether the quality of implementation may vary enough to affect the results. Variability in the quality of care provided by the control groups in the various studies may also have an impact on the apparent effectiveness of the intervention.

Conclusion

Overall, this review suggests that these interventions do reduce the use of inpatient services. However, the improvements associated with these early intervention programs may not be specific to them.[37] It has been argued that increasing funding for psychosis treatment would also provide a similar effect without using the treatment ethos of these ACT-based services. Future research should attempt to utilize larger RCT studies to examine which specific components of these early intervention programs are beneficial and which may be unnecessary. One area of concern for future research is whether the improvement afforded by these intervention programs can be maintained beyond the first few years. Some research has suggested that the gains from early intervention fade after the patients leave the program.[11,38] Potential research could examine whether expanding the length of treatment (perhaps indefinitely if needed), or development

of post-intervention services for long-term follow-up are effective at maintaining these treatment benefits.

Supplementary Material

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