Reducing the Duration of Untreated Psychosis (DUP) in a US Community: A Quasi-Experimental Trial

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Objective: Duration of Untreated Psychosis (DUP) remains unacceptably long and limits effectiveness of care. To determine whether an early detection campaign ("Mindmap") can reduce DUP in a US community setting. *Methods:* In this nonrandomized controlled trial, Mindmap targeted the catchment of one specialty first-episode service or FES (STEP, Greater New Haven) from 2015 to 2019, while usual detection efforts continued at a control FES (PREP, Greater Boston). Mindmap targeted diverse sources of delay through mass & social media messaging, professional outreach & detailing, and rapid enrollment of referrals. Both FES recruited 16–35 years old with psychosis onset ≤3 years. Outcome measures included *DUP-Total* (onset of psychosis to FES enrollment), *DUP-Demand* (onset of psychosis to first antipsychotic medication), and *DUP-Supply* (first antipsychotic medication to FES enrollment). *Results:* 171 subjects were recruited at STEP and 75 at PREP. Mindmap was associated with an increase in the number of referrals and in efficiency of engagement at STEP. Pre-campaign DUP (2014–2015) was equivalent, while Mindmap was associated with DUP reductions at STEP but not PREP. *DUP-Total* fell significantly in both the first and the second quartile (11.5 and 58.5 days reduction per campaign year, respectively). *DUP-Demand* and *DUP-Supply* fell in the third quartiles only (46.3 and 70.3 days reduction per campaign year, respectively). No reductions were detectable across all quartiles at PREP, but between site comparisons were not significant. *Conclusions:* This is the first controlled demonstration of community DUP reduction in the US, and can inform future early detection efforts across diverse settings.

Key words: early detection (ED)/early intervention services (EIS)/first-episode psychosis (FEP)/first-episode services (FES)/population health/pathways to care/schizophrenia/coordinated specialty care (CSC)

Introduction

The interval between psychosis onset and treatment, or the Duration of Untreated Psychosis (DUP), is marked by severe distress,[1] aversive pathways to care,[2] increased risks for suicide,[3] aggression,[4] and criminal justice involvement.[5] Longer DUP is associated with poorer outcomes across healthcare systems, despite variability in definition and measurement.[6–8]

Prior efforts to reduce DUP, or early detection (ED), have delivered mixed results.[9,10] Possible causes of prior failures to demonstrate significant effects include premature termination of campaigns, or interventions that were either too narrowly or inaccurately targeted at posited sources of delay. In contrast, the pioneering Scandinavian Treatment and Intervention in Psychosis (TIPS) campaign reduced DUP across two healthcare sectors in comparison to two control sectors (median 5 vs. 16 weeks).[11] TIPS combined a broad public education campaign with specific teams that rapidly assessed and connected referrals to clinical services. DUP reduction was associated with

improvements in distress, symptom severity[11] and suicidality at enrollment,[12] negative symptoms 5 years later,[13] and recovery (31 vs. 15%) 10 years later.[14] Notably, an unanticipated interruption of the campaign for over a year, delivered a natural experiment wherein DUP decayed toward control levels.[15] A subsequent effort in Singapore used a similarly multifocal campaign to successfully reduce DUP, albeit compared to a historical control.[16]

Significant differences in population characteristics and healthcare delivery, and subsequent changes in the media environment, limit simple extrapolation of these successful interventions to current US settings. Also, the maturation of an international evidence base for specialty team-based first-episode services (FES),[17] along with concerns that prolonged DUP could reduce their effectiveness,[18] highlights the need for an updated approach. Effective ED when combined with such FES can target the "critical period" or the 3–5 years after psychosis onset wherein the majority of functional losses accrue[19] to deliver population-based early intervention services to better target long term morbidity in Schizophrenia.[20]

Review of historical data from our FES[21,22] suggested several missed opportunities during the pathway to care, including suicide attempts, police interactions,[23] and involuntary admissions.[21] Also, the myriad routes taken to our clinics, involving multiple community members, motivated a multi-pronged and regionally tailored ED intervention.

The guiding question for this study was: Can an early detection campaign reduce DUP across a US community? We hypothesized that DUP would be reduced for enrollees at the FES serving the geographic catchment targeted by an ED campaign, but remain unchanged for enrollees at a control FES where usual detection would continue.

Methods

This nonrandomized controlled study measured DUP for consecutive admissions to two equivalent FESs located in Boston, Massachusetts (PREP) and New Haven, Connecticut (STEP) for 1 year before (Feb 1, 2014–Jan 31, 2015), and during a 4-year (Feb 1, 2015–Jan 31, 2019) early detection campaign (titled *Mindmap*) targeting STEP's catchment. A study protocol detailing the design and analytic approach was published prior to implementation.[24] All data was collected prior to the onset of the COVID-19 pandemic. Per oversight by Yale & Beth Israel Deaconess Human Investigations Committees, all subjects provided written informed consent after receiving a complete description of the study.

Setting and Choice of Control Site

The two FESs shared important structures, processes, and cultures of care. Both STEP (New Haven, Connecticut)

and PREP (Boston, Massachusetts) operate within public-academic collaborations between the respective State Mental Health Agencies and University Departments of Psychiatry[22,25] with a mission to serve early course psychosis patients regardless of health insurance or legal status. Also, both US states had, several years prior to this study, enacted equivalent and progressive expansions of publicly funded healthcare.[26] Finally, each FES shared leadership and intake procedures with affiliated prodrome or clinical high-risk (CHR) programs. STEP's target catchment comprised 10 towns (population ~400,000) within Greater New Haven, while PREP served a comparable population within metropolitan Boston. While Connecticut and Massachusetts share a border, the two FESs were distinct from a campaign perspective i.e., no overlaps in referral networks, or in regional media markets.

Design of the Early Detection Campaign ("Mindmap")

Conceptual Model. Pathways to care were envisioned across two successive phases of delay. The time from onset of psychosis to first use of antipsychotic medication defined the "Demand" side of the pathway. This can include one or more of several overlapping and modifiable, sources of delay e.g., in the identification or appropriate attribution (by patients or family members) of unusual experiences or behaviors to illness, acknowledgment of the need for care, initiation of help-seeking, or recognition of psychosis by a clinician. The date of first antipsychotic medication serves as a reliable proxy for identification of psychosis by a healthcare professional, and thus the end of the Demand side. This is usually followed by further delays within the healthcare system e.g., in referral to, and eventual enrollment in the local FES, that comprise the "Supply" side of overall DUP.

Mindmap targeted both demand and supply side source of delay, was deliberately agnostic in its prior weighting of each as a source of delay, and used a *social-ecological* model[27] to continuously adapt campaign tactics to the responsiveness of all relevant stakeholders involved in patients' pathways to care. These were categorized into separate sectors or groups[24] (e.g. potential patients, their peers and family members, community and clinical agencies, clergy, colleges and high schools, judicial system, local government) for whom targeted messaging was developed, even as they were viewed as members of a putative regional *network* that could collaborate with each other and STEP to transform local pathways to care.[20] A young person's entry into care was expected to involve several, and sometimes repetitive, contacts across this network. In contrast to linear models of behavior change that require some level of illness awareness within a patient for successful help-seeking,[24] these contacts were valued as offering multiple and diverse opportunities to connect ambivalent or even unwilling individuals to

STEP ("no wrong door"). The clinic in turn aimed to respond in a rapid, proactive, and persistent manner to facilitate admission.

Intervention. Three components were integrated under a common brand ("*Mindmap*") with a unified call to action (referral phone number) and implemented over 4 years (Feb 1, 2015–Jan 31, 2019). While detailed separately,[24] key elements are summarized below:

Public Education Messaging was developed for lay and professional audiences in consultation with a marketing firm. These were channeled via multiple social and mass media channels (newspaper, transit and cinema advertisements, postcards, billboards) (Supplementary figures SF1 and SF2). Signs and symptoms of psychosis were accompanied by simple, visually attractive text and graphics targeting the information needs of previously identified stakeholder groups, and linked to a campaign website with continuously refreshed content. A variety of social media channels (Facebook, Twitter, YouTube, Instagram, Reddit, LinkedIn) were used to tailor messaging to specific groups (e.g. to college students at freshman orientation) (Supplementary videos SV1–SV3). A variety of social media metrics, including passive impressions and interactions with campaign messaging (e.g. clicking or sharing) were monitored to assess reach, and continuously refine messaging.

Outreach & Detailing *Mindmap* hosted (e.g. informational dinners with invitations to all stakeholders at local restaurants) and participated (e.g. information booth at Annual Road Race) in community events as part of a general effort to raise awareness of the campaign. These were followed by detailing of specific contacts made via visits to workplaces and ongoing phone and email contact. This aimed to build and sustain referral relationships in an expanding local network that was monitored for broad inclusion of stakeholder groups within and outside the healthcare sector. Specific giveaway materials with consistent campaign messaging were tailored to these groups (e.g. tear-off information sheets requested by police officers).

Rapid Access to STEP (RAS) A single referral number attached to a mobile phone was set up with an expected response time of one day. All queries were reviewed weekly by a team consisting of the outreach coordinator, FES clinical lead, and program director. An explicit quality improvement framework was used to review informative outliers and implement process improvements to limit all sources of delay between the first call and enrollment into STEP, with a performance standard of <1 week. Also, noneligible calls were reviewed to inform refinements in messaging across the other two campaign components.

Eligibility Criteria and Intake Procedures

Inclusion criteria were made simple to limit referral delay, focus on early course illness, and remain consistent with historical practice at both FESs: all individuals within three years of psychosis onset, between 16–35 years of age, and living in the target catchment were offered care. We excluded those with psychosis secondary to a previously established medical illness, affective or substance use disorder, and those unable to communicate in English or provide meaningful informed consent (due to cognitive limitations or pre-trial mandates for treatment). We also excluded from this study (but not from FES care) individuals with new onset psychosis who were already in care at an affiliated CHR program prior to February 2014.

Measuring DUP & Pathways to Care

The Structured Interview for Psychosis-risk Syndromes (SIPS, version 5.3)[28] was used to confirm and date transition to psychosis, defined as meeting the Presence of Psychotic Syndrome (POPS) criteria i.e., at least 6 in severity on scales P1-P5 of SIPS, with at least one of these symptoms occurring over a period of one month for at least one hour per day at a minimum average frequency of 4 days per week, or leading to serious disorganization or dangerousness. The POPS date was determined with input from all available stakeholders in the pathway to care, identified within a structured questionnaire.[29] A modified Pathways to Care instrument[29] was used to track each help-seeking episode, beginning with the onset of psychotic symptoms and concluding upon arrival to the FES (STEP or PREP). A medication questionnaire was used to date first use of an antipsychotic medication for psychosis (i.e. excluding off-label uses). The date of enrollment to STEP/PREP defined the beginning of FES care.

These data were used to generate three measures of DUP consistent with the design: *DUP-Demand* (onset of psychosis to first antipsychotic), *DUP-Supply* (first antipsychotic to enrollment in FES), and *DUP-Total* (onset of psychosis to enrollment in FES). For those patients entering FES without prior antipsychotic exposure, *DUP-Supply* was set to zero, and *DUP-Demand* and *DUP-Total* were identical.

Weekly calls with staff across both sites included structured presentations of each enrolled case with consensual confidence ratings of DUP (High, Medium, or Low) based on a rubric that considered the quality of information from the patient and collateral sources. At least one investigator from each site was present on all calls, and ambiguity or disagreements were resolved by case review after one month to allow time for additional collateral and/or better information from a more symptomatically stable patient.

Other Measures & Procedures

A detailed questionnaire adapted from prior studies (21) was used to assess for demographic variables and socioeconomic class. Modified CONSORT flow sheets were used to monitor all calls to each FES with usable contact information (*Inquiries*), from which potential subjects were contacted (*Assessed for eligibility*), followed by detailed tracking of those who were either *Excluded, Eligible but refused* participation, *Lost to enrollment* before eligibility could be confirmed, or *Enrolled*. When one exclusionary criterion was met, not all other criteria could be consistently captured, resulting in overlapping counts within this category (Supplementary tables S1–S3). Annual review of outreach activities at the control site was used to confirm usual detection.

Statistical Analysis

A detailed protocol including planned analyses was published prior to initiation of the campaign.[24] Descriptive statistics such as mean and standard deviation, median, IQR and range, frequency, and percentage were used to summarize patients' characteristics by site, pre- and postcampaign. It is well-known that DUP distributions are right-skewed. Therefore, two-way analysis of variance (two-way ANOVA) using log-transformed data was planned. However, we conceptualized this skewness as indicating heterogeneous underlying causes of treatment delay across the DUP distribution that would not be adequately captured by statistical models based on mean estimates. Consistent with this *a priori* expectation of differential impact across the DUP distribution, we applied quantile regression (QR) to parse campaign effects over time and across the full range of DUP. QR does not rely on a normality assumption, and thus provides more accurate estimates in samples with extreme outliers.[30] Also, QR examines effects on conditional quantiles instead of conditional means, allowing evaluation of varied impact of ED across DUP distributions. We simulated[31] and validated this in an independent sample from TIPS.[32] Significance levels were set at $P < .05$ (two-sided). SAS 9.4 (Cary, NC) was used to conduct all analyses.

Results

Subject Flow

There was a progressive yearly increase in community responsiveness to the campaign. This included increases in digital impressions (totaling >4 million), activity within multiple social media messaging threads (Facebook, Twitter, YouTube), and traffic to the campaign website, with >35,000 visits attributed to unique digital users within STEP's geographic catchment. This was reflected in escalating inquiries to the referral phone line, from a pre-campaign baseline of 101 to an average of 314 per year, with completed eligibility assessments increasing

from 98 to 263 per year during the campaign years. At PREP both inquiries (97 vs. 108 per year) and assessments (25 vs. 30 per year) continued at a steady pace across the baseline and campaign years [Supplementary tables S1–S3]. There were also significant differences across sites in terms of efficiency in enrollment. During the campaign years at STEP, fewer patients were lost to enrollment (5/1050 or 0.5% vs. 22/119 or 18.5% at PREP), and of those confirmed to be eligible, fewer declined participation (16/163 or 9.8% vs. 13/75 or 17% at PREP). The estimated DUP-Total for those who declined did not differ from other enrollees at STEP (median 242.5 days, $P = .56$) or at PREP (median 347 days, $P = .84$). A significant proportion of ineligible calls fielded by STEP during the campaign (322/822 or 37%) were inquiries about behavioral health services for individuals without a psychotic disorder.

Enrolled Sample

STEP and PREP recruited samples that were comparable, diverse, and reflective of local demography (table 1). Overall, these were young (mean age 22.2 years, SD 3.5) and predominantly male (71%) patients. A significant proportion identified as first-generation immigrants (17%).

Duration of Untreated Psychosis

Patients enrolled via usual detection pathways at STEP and PREP suffered comparable delay during

Table 1. Characteristic of enrollees to FES (2014–2019)

	STEP (*n* = 171)	PREP[R] (*n* = 75)	*P* value
Age, Mean (SD) in years	22.5 (3.8)	21.8 (2.8)	.15
Gender			.77
Male	120 (70.2%)	54 (72.0%)	
Female	51 (29.8%)	21 (28.0%)	
First language			.33
English	138 (80.7%)	56 (74.7%)	
Spanish	15 (8.8%)	6 (8.0%)	
Other	18 (10.5%)	13 (17.3%)	
Race			.22
White	58 (33.9%)	21 (28.0%)	
Black	76 (44.4%)	34 (45.3%)	
Interracial	27 (15.8%)	10 (13.3%)	
Other	10 (5.8%)	10 (13.3%)	
Hispanic/Latino			.72
NO	138 (80.7%)	62 (82.7%)	
YES	33 (19.3%)	13 (17.3%)	
Born in USA			.07
NO	25 (14.6%)	18 (24.0%)	
YES	146 (85.4%)	57 (76.0%)	
Education			
Years of education (M+/- SD)	12.6 (2.0)	12.5 (1.8)	.62
Grade school	144 (84.2%)	66 (88.0%)	.44
College and above	27 (15.8%)	9 (12.0%)	

Table 2. DUP (days) for patients enrolled in FES (STEP & PREP) before (2014–2015) and during (2015–2019) early detection campaign (Mindmap)

		STEP		PREP	
		2014–2015 (pre-Mindmap) N = 24	2015–2019 (Mindmap) N = 147	2014–2015 N = 12	2015–2019 N = 63
DUP-Demand	Mean (SD)	173.5 (177.2)	145.3 (234.0)	204.1 (211.4)	186.4 (236.7)
	Median (Q1,Q3)	98.5 (19.5, 329.0)	48.0 (14.0, 183.0)	127.0 (46.5, 317.5)	81.0 (17.0, 291.0)
	Range	0–700	0–1153	1–701	1–938
DUP-Supply	Mean (SD)	153.0 (218.7)	138.7 (242.2)	180.8 (175.5)	297.8 (312.6)
	Median (Q1, Q3)	29.5 (13.5, 246.0)	20.0 (9.0, 133.0)	152.0 (39.0, 234.5)	149.0 (65.0, 458.0)
	Range	0–726	0–1106	0–521	0–1290
DUP-Total	Mean (SD)	326.5 (303.4)	284.1 (301.6)	384.9 (255.4)	484.2 (346.6)
	Median (Q1, Q3)	311.5 (59.0, 492.5)	149.0 (50.0, 457.0)	324.5 (224.5, 526.5)	430.0 (162.0,709.0)
	Range	8–1060	2–1189[†]	19–917	13–1416[†]

[†]0–1087 (PREP) and 0–1094 (STEP) after excluding those with DUP-Total > 3 years.
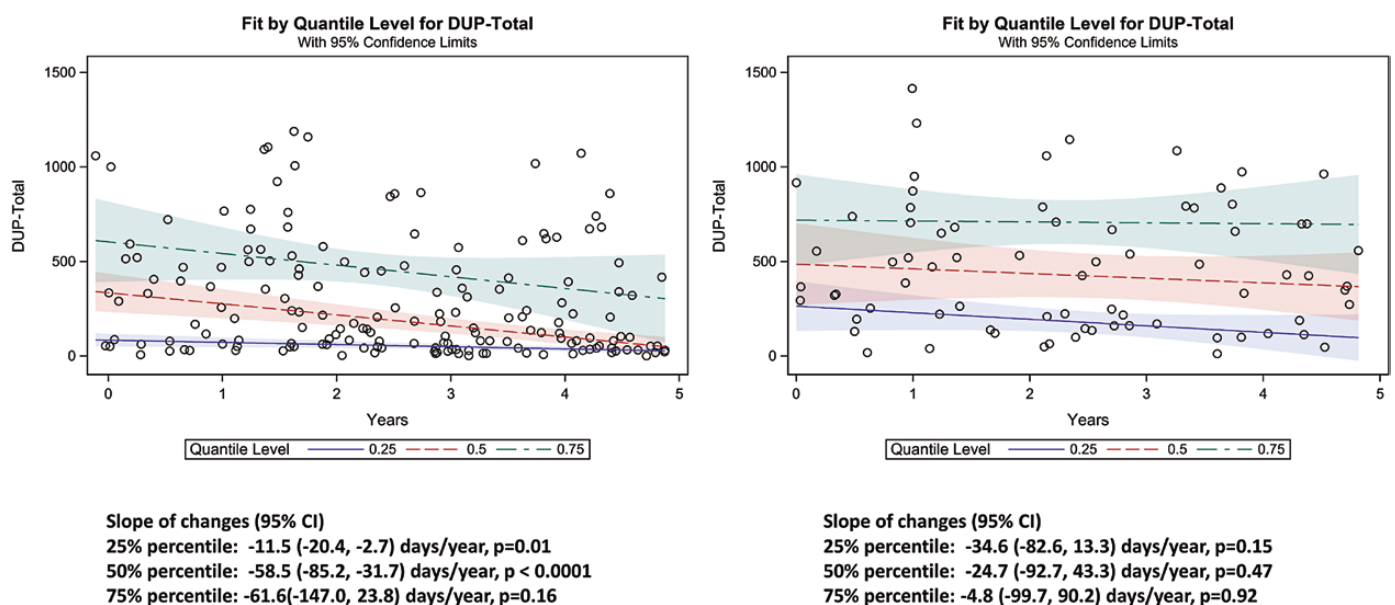

Fig. 1. Change in *DUP-Total* over time at Intervention (STEP, left panel) and Control (PREP, right panel) site.

the pre-campaign year (table 2). As expected, the DUP distributions were skewed, but equivalent at both sites (median *DUP-Total* 311.5 days, IQR: 59–492.5 at STEP vs. 324.5 days, IQR: 224.5–526.5 at PREP, *P* = .50).

Two-way ANOVA using log-transformed DUP detected neither a significant site by campaign interaction, nor main effects of site or campaign (*P* values of interaction: 0.60, 0.23, 0.39, for *DUP-Demand, DUP-Supply,* and *DUP-Total* respectively). Planned QR analysis revealed campaign associated downward temporal trends across the distribution for all three measures of delay. At STEP, reductions in *DUP-Total* met conventional significance (*P* < .05) in both the first quartile (Q1, 11.5 days reduction per campaign year) and second quartile (Q2, 58.5 days reduction per campaign year), but not in the third quartile of the distribution (Q3, 61.6 days reduction

per campaign year, *P* = .16) (figure 1). Reductions in *DUP-Demand* (46.3 days reduction per campaign year) (figure 2), and *DUP-Supply* (70.3 days reduction per campaign year) (figure 3) were both significant in Q3. No reductions were detectable across all quartiles at the control (PREP) site. Of note, quantiles are based on ranking of data. This means that although for any individual subject *DUP-Total=DUP-Demand + DUP-Supply*, groups of subjects in the same quartile for *DUP-Total* are not necessarily ranked in the same order for *DUP-Demand* or *DUP-Supply*. For example, subjects ranked within Q3 of *DUP-Total* may include those with a shortened *DUP-Demand* and lengthened *DUP-Supply* or, conversely others with a lengthened *DUP-Demand* and shortened *DUP-Supply*. This explains why the significant reductions observed in Q3 of both *DUP-Demand* and *DUP-Supply*
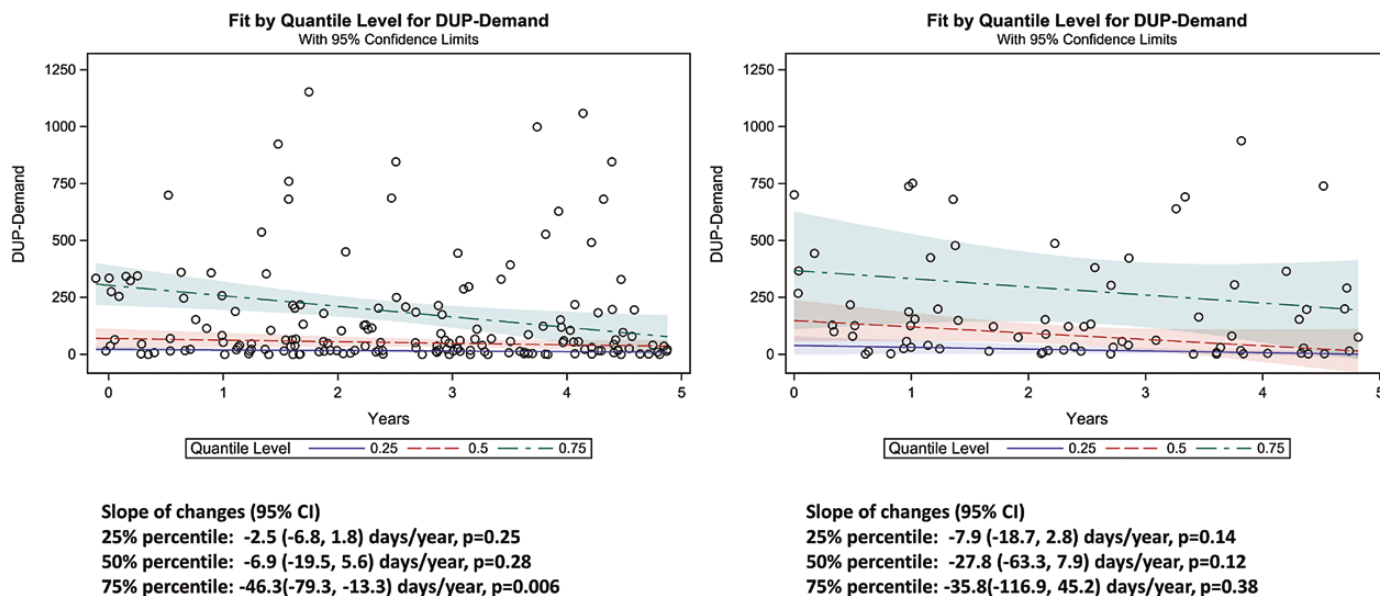
Fig. 2. Change in *DUP-Demand* over time at Intervention (STEP, left panel) and Control (PREP, right panel) site.
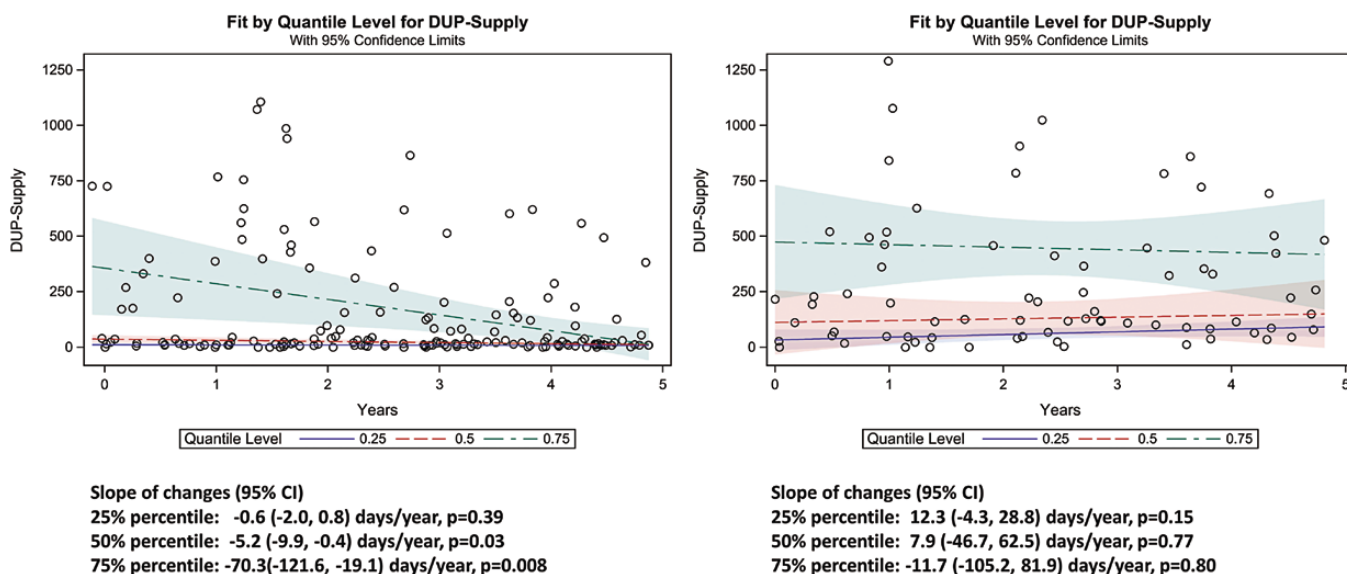

Fig. 3. Change in *DUP-Supply* over time at Intervention (STEP, left panel) and Control (PREP, right panel) site.

at STEP are compatible with a nonsignificant decrease in Q3 of *DUP-Total*.

DUP Confidence ratings were available for all except one subject, only 18 of 245 were of low confidence, and equally infrequent at both sites. When these low confidence DUP estimates were excluded from the analysis, DUP-Total reductions at STEP acquired significance in Q3 (73.5 days, $P = .046$) with all other improvements preserved. Six subjects (3 at each site) were determined after enrollment to have DUP-Total beyond the exclusion criteria of 3 years (ranging from 1106 to 1416 days). Their data was retained within the intention to analyze all enrolled subjects, but re-analysis after exclusion did not meaningfully change the magnitude or significance of the results.

Discussion

Mindmap progressively reduced the Duration of Untreated Psychosis in a US community. While there were temporal trends of reduction across all quartiles of the DUP distribution at the early detection site, statistically significant reductions could be quantified in specific quartiles over the 4-year campaign. Time from psychosis onset to enrollment at STEP (*DUP-Total*) fell by 11.5 days per campaign year for the first quartile, and by almost two months (58.5 days) per campaign year for the second quartile (median). The time from psychosis onset to first antipsychotic prescription (*DUP-Demand*) was reduced in the third quartile by 46 days per campaign year, while subsequent delay

to enrollment at STEP (*DUP-Supply*) progressively fell in the third quartile by 70 days per campaign year. These reductions confirmed that the campaign modified sources of delay both prior to and after identification of psychosis by a healthcare provider, and the differentiated effect across the care pathway validated the multi-focal design of Mindmap. No contemporaneous changes in DUP were detected at the control site. Given skewed DUP distributions, central measures can mislead, but for ease of comparison to other studies, while *DUP-Total* was comparable across both sites at baseline, it fell at the ED site from a median of 312 to 149 days (44.5 to 21 weeks or 10 to 5 months).

In terms of comparisons to equivalent studies, TIPS is the only other initiative that has successfully reduced community DUP with a contemporaneous control. At the end of TIPS's 3-year campaign, the two ED sectors reported a third of delay in the non-ED sectors (median 5 vs. 16 weeks in control sectors).[11] The equivalent results for this study are relatively similar with *DUP-Total* at STEP (median 21 vs. 61 weeks at PREP), albeit with longer absolute delays. TIPS did not exclude for DUP >3 years and was thus able to demonstrate a larger magnitude of reduction in the third quartile (41 weeks), but a comparable reduction in the second quartile (11 weeks).[32] The largest US FES sample (with usual detection) reported a median DUP of 74 weeks[33] which is longer but comparable to our control site median *DUP-Total* of 61 weeks.

A significant caveat is related to differential enrollment across the two sites. *Mindmap* led to a three-fold increase in referrals and a "stickier" front door at STEP i.e., both fewer referrals lost before eligibility could be confirmed, and fewer refusals amongst those eligible for FES. In contrast, losses to enrollment at the control site, while illustrative of another disadvantage of usual detection, resulted in underpowered between site comparisons for DUP.

Several sources of both systematic error (i.e. biases in design and confounding variables) and random error were considered in this test of ED.[34] Could unknown stochastic changes impacting healthcare access better explain the observed reduction in DUP (rather than the campaign)? This is unlikely given a meaningfully similar and contemporaneous control (PREP) site wherein DUP remained stable and comparable to historical levels, and progressive reductions at STEP over 4 years (as would be expected for a campaign that expands its reach across a local network). Did *Mindmap* simply divert newer onset cases to STEP rather than reduce true community DUP? If so, DUP would have risen at other regional providers during the campaign (even as it fell at STEP): unfortunately, we were unable to gain access to DUP data from such "sentinel" sites as planned.[24] However, several factors make such sampling bias unlikely. STEP was an established regional clearinghouse for referrals for almost a decade prior to the campaign, and during Mindmap fielded inquiries from an expanding variety of referral sources, with a persistently wide range of DUP, making the recruited sample likely more, not less representative of recent onset psychosis in the target catchment.

The retrospective dating of psychosis onset is inescapably fraught with limitations of memory (in patients and caregivers) and medical records. However, the use of the SIPS with the Pathways to Care scale allowed systematic and longitudinal assessments that began with the onset of prodromal symptoms and ended with enrollment at an FES, and identified caregivers and stakeholders along the care pathway who were valuable sources of collateral information. This approach resulted in very few low confidence DUP assessments across both sites (7%), and exclusion of these cases did not impact the overall results. Notably, the use of the SIPS offers several advantages. Explicit operationalization of a threshold for psychosis (via POPS criteria) supports reliable (i) dating of DUP and (ii) delineation from CHR, allowing analysis of the impact of DUP reduction on subsequent outcomes that is less confounded by inclusion of prodromal samples. Also, (iii) the dating of prodromal states in those with established psychosis, can provide useful information, such as on distinct help-seeking profiles, that can inform refinements in future ED campaigns.[2] Also, we validated these conversion criteria in a separate CHR sample who, after meeting POPS conversion to psychosis criteria, looked very similar to a matched FES sample in terms of illness severity one year later.[35]

Other notable design features included the exclusion of subjects from this analysis who had already been recruited by local CHR clinics prior to this study, to avoid a source of sampling bias (i.e. including DUP = O subjects who had not been recruited by the FESs). Finally, the use of quantile regression allowed for more granular analyses of campaign effects across the entire DUP distribution, and over time.

We restricted eligibility to those with psychosis onset within the prior 3 years for pragmatic and conceptual reasons. First, we needed to optimize the impact of our FES with limited capacity on reducing access delays across a large target population. Second, prior observational data suggest that the first 3–5 years after psychosis onset is a "critical period" wherein much of eventual functional decline occurs, and during which assertive treatment models may have the most impact.[36] Indeed, this has served as an organizing premise for early intervention services worldwide.[37] However, this strategy comes with clear disadvantages. There is no evidence of a threshold DUP beyond which FES lose their additional value, and it is thus possible that some patients were denied this benefit. However, various analyses have suggested diminishing returns for specialized care as DUP increases.[18,38,39] Nevertheless, more generous funding models for FES could allow wider inclusion with the empirically driven adjustments to illness duration over time.

Are these results generalizable? Both STEP and PREP are academically affiliated FES with longstanding early intervention services but are integrated within 2 of 50

nationwide State Mental Health Agencies that have historically served the majority of individuals with chronic, serious mental illness in the US[40] and as such provide a nationally relevant platform for early intervention services.[25] However, as public-sector services, both PREP and STEP could sustain outreach and extended engagement efforts with prospective patients, and these are activities that are unbillable and therefore fiscally disincentivized in most healthcare organizations. Also, the catchments were predominantly urban and suburban with pathways that may not reflect the realities of many rural communities.

Are these results sustainable? The temporal trends of progressive reduction of DUP suggest that prolongation of the campaign would have further reduced DUP. Ongoing assessments of postcampaign admissions at STEP will permit future analysis of the durability of *Mindmap's* impact on both the demand and supply sides of regional pathways to care and DUP.

How can these results inform future study designs of early detection? The considerable heterogeneity across prior ED trials in terms of sampling, intervention design, and measurement[10] has limited the usefulness of quantitative aggregation or meta-analysis. While several studies failed to show an effect, this may have been due to an excessively narrow focus on demand or supply side contributors to overall DUP, prematurely terminated campaigns, or insensitivity of the analytic approach wherein the inappropriate use of mean or median summary estimates for skewed DUP distributions produced Type II errors. For example, our re-analysis of TIPS data revealed that much of the overall reduction in DUP was explained by that campaign's effect on the longer end of the DUP distribution, and in males.[32] Thus a chance variation in a smaller sample or a shorter campaign could lead to erroneously null results. Such an effect may have occurred in one prior effort wherein longer DUP subjects were preferentially recruited to an FES that hosted a short, one-year campaign.[41] Our results support sustained, multi-focal interventions with careful parsing of effects across the full range of the DUP distribution.

How can these results inform future implementations of ED? Our adaptation of elements from a Scandinavian setting to a US catchment offers its own example of knowledge transfer across diverse settings, but there are specific aspects worth emphasizing. We used a *generic* campaign framework[24,42] that was able to apply lessons from TIPS, but tied this to *specific* components that were designed to adaptively respond to feedback from the local referral network. Thus Mindmap was a complex intervention[43–45] and especially suited to fragmented healthcare delivery systems where the source or magnitude of delay may only become apparent after, or in response to, intervention or ED efforts. Such an approach to campaign design can accommodate the need to continuously adapt tactics to local networks, while retaining an overall strategic template that is portable across settings. The complex design however does

severely limit inferences about "active ingredients" or specific components that proved most effective. These are best interrogated in subsequent disaggregation studies, but will also be forthcoming in future analyses from our dataset (e.g. evaluating the specific effect of the quality improvement style RAS component on wait times to our FES).

The onset of psychosis too often initiates a "destructive chaos" wherein subjective distress interacts with unnecessarily long and aversive pathways to care.[46] The integration of early detection within expanding implementations of first-episode services offers the prospect of comprehensive early intervention services that will address an urgent gap in population health.[20]

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

References

1. Schalkwyk GI van, Davidson L, Srihari V. Too late and too little: narratives of treatment disconnect in early psychosis. *Psychiatr Q*. 2015:1–12.
2. Ferrara M, Guloksuz S, Mathis WS, *et al.* First help-seeking attempt before and after psychosis onset: measures of delay and aversive pathways to care. *Soc Psychiatry Psychiatr Epidemiol*. 2021;56(8):1359–1369.
3. Barrett EA, Sundet K, Faerden A, *et al.* Suicidality before and in the early phases of first episode psychosis. *Schizophr Res*. 2010;119(1-3):11–17.
4. Large M, Nielssen O. Evidence for a relationship between the duration of untreated psychosis and the proportion of

psychotic homicides prior to treatment. *Soc Psychiatry Psychiatr Epidemiol.* 2008;43(1):37–44.

5. Wasser T, Pollard J, Fisk D, Srihari V. First-episode psychosis and the criminal justice system: using a sequential intercept framework to highlight risks and opportunities. *Psychiatr Serv.* 2017;68(10):994–996.

6. Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am J Psychiatry.* 2005;162(10):1785–1804.

7. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Arch Gen Psychiatry.* 2005;62(9):975–983.

8. Penttilä M, Jääskeläinen E, Hirvonen N, Isohanni M, Miettunen J. Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry.* 2014;205(2):88–94.

9. Lloyd-Evans B, Crosby M, Stockton S, *et al.* Initiatives to shorten duration of untreated psychosis: systematic review. *Br J Psychiatry.* 2011;198(4):256–263.

10. Oliver D, Davies C, Crossland G, *et al.* Can we reduce the duration of untreated psychosis? A systematic review and meta-analysis of controlled interventional studies. *Schizophr Bull.* 2018;44(6):1362–1372.

11. Melle I, Larsen TK, Haahr U, *et al.* Reducing the duration of untreated first-episode psychosis: effects on clinical presentation. *Arch Gen Psychiatry.* 2004;61(2):143–150.

12. Melle I, Johannesen JO, Friis S, *et al.* Early detection of the first episode of schizophrenia and suicidal behavior. *Am J Psychiatry.* 2006;163(5):800–804.

13. Larsen TK, Melle I, Auestad B, *et al.* Early detection of psychosis: positive effects on 5-year outcome. *Psychol Med.* 2011;41(7):1461–1469.

14. Hegelstad WT, Larsen TK, Auestad B, *et al.* Long-term follow-up of the TIPS early detection in psychosis study: effects on 10-year outcome. *Am J Psychiatry.* 2012;169(4):374–380.

15. Joa I, Johannessen JO, Auestad B, *et al.* Effects on referral patterns of reducing intensive informational campaigns about first-episode psychosis. *Early Interv Psychia.* 2007;1(4):340–345.

16. Chong SA, Mythily S, Verma S. Reducing the duration of untreated psychosis and changing help-seeking behaviour in Singapore. *Soc Psychiatry Psychiatr Epidemiol.* 2005;40(8):619–621.

17. Correll CU, Galling B, Pawar A, *et al.* Comparison of early intervention services vs treatment as usual for early-phase psychosis. *JAMA Psychiatry*. 2018;75(6):555–565. doi: 10.1001/jamapsychiatry.2018.0623

18. Kane JM, Robinson DG, Schooler NR, *et al.* Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE Early Treatment Program. *Am J Psychiatry.* 2016;173(4):362–372.

19. Birchwood M, Todd P, Jackson C. Early intervention in psychosis. The critical period hypothesis. *Br J Psychiatry Suppl.* 1998;172(33):53–59.

20. Srihari VH, Jani A, Gray M. Early intervention for psychotic disorders: building population health systems. *JAMA Psychiatry.* 2016;73(2):101–102.

21. Srihari VH, Tek C, Kucukgoncu S, *et al.* First-episode services for psychotic disorders in the U.S. public sector: a pragmatic randomized controlled trial. *Psychiatr Serv.* 2015;66(7):705–712.

22. Caplan B, Zimmet SV, Meyer EC, *et al.* Prevention and recovery in early psychosis (PREP(®)): building a public-academic partnership program in Massachusetts, United States. *Asian J Psychiatr.* 2013;6(2):171–177.

23. Pollard JM, Ferrara M, Lin IH, *et al.* Analysis of early intervention services on adult judicial outcomes. *JAMA Psychiatry.* 2020;77(8):871–872.

24. Srihari VH, Tek C, Pollard J, *et al.* Reducing the duration of untreated psychosis and its impact in the U.S.: the STEP-ED study. *BMC Psychiatry.* 2014;14:335.

25. Srihari VH, Breitborde NJ, Pollard J, *et al.* Public-academic partnerships: early intervention for psychotic disorders in a community mental health center. *Psychiatr Serv.* 2009;60(11):1426–1428.

26. Frank RG. Realizing the promise of parity legislation for mental health. *JAMA Psychiatry.* 2017;74(2):117–118.

27. Stokols D. Translating social ecological theory into guidelines for community health promotion. *Am J Health Promot.* 1996;10(4):282–298.

28. McGlashan TH, Miller TJ, Woods SW, Rosen JL. *Structured Interview for Prodromal Syndromes (SIPS)*. New Haven: Yale University; New Haven; 2001.

29. Judge AM, Perkins DO, Nieri J, Penn DL. Pathways to care in first episode psychosis: a pilot study on help-seeking precipitants and barriers to care. *J Ment Health*. 2005;14(5):465–469.

30. Buchinsky M. Recent advances in quantile regression models: a practical guideline for empirical research. *J Hum Resour*. 1998;33(1):88–126.

31. Guloksuz S, Li F, Tek C, *et al.* Analyzing the duration of untreated psychosis: quantile regression. *JAMA Psychiatry.* 2016;73(10):1094–1095.

32. Ferrara M, Guloksuz S, Li F, *et al.* Parsing the impact of early detection on duration of untreated psychosis (DUP): applying quantile regression to data from the Scandinavian TIPS study. *Schizophr Res.* 2019;210:128–134.

33. Addington J, Heinssen RK, Robinson DG, *et al.* Duration of untreated psychosis in community treatment settings in the United States. *Psychiatr Serv.* 2015;66(7):753–756.

34. Friis S, Larsen TK, Melle I, *et al.* Methodological pitfalls in early detection studies – the NAPE Lecture 2002. *Acta Psychiatrica Scandinavica*. 2003;107(1):3–9.

35. Yoviene Sykes LA, Ferrara M, Addington J, *et al.* Predictive validity of conversion from the clinical high risk syndrome to frank psychosis. *Schizophr Res.* 2020;216:184–191.

36. Birchwood M, Todd P, Jackson C. Early intervention in psychosis. The critical period hypothesis. *Br J Psychiatry Suppl.* 1998;172(33):53–59.

37. Srihari VH, Shah J, Keshavan MS. Is early intervention for psychosis feasible and effective? *Psychiatr Clin North Am.* 2012;35(3):613–631.

38. Cechnicki A, Cichocki Ł, Kalisz A, Błądziński P, Adamczyk P, Franczyk-Glita J. Duration of untreated psychosis (DUP) and the course of schizophrenia in a 20-year follow-up study. *Psychiatry Res.* 2014;219(3):420–425.

39. Howes OD, Whitehurst T, Shatalina E, *et al.* The clinical significance of duration of untreated psychosis: an umbrella review and random-effects meta-analysis. *World Psychiatry.* 2021;20(1):75–95.

40. Frank RG, Glied SA. *Better But Not Well: Mental Health Policy in the United States Since 1950*. Baltimore, MD: Johns Hopkins University Press Books; 2006.

41. Krstev H, Carbone S, Harrigan SM, Curry C, Elkins K, McGorry PD. Early intervention in first-episode psychosis–the impact of a community development campaign. *Soc Psychiatry Psychiatr Epidemiol.* 2004;39(9):711–719.

42. Noar SM, Zimmerman RS. Health Behavior Theory and cumulative knowledge regarding health behaviors: are we moving in the right direction? *Health Educ Res.* 2005;20(3):275–290.

43. Shiell A, Hawe P, Gold L. Complex interventions or complex systems? Implications for health economic evaluation. *BMJ.* 2008;336(7656):1281–1283.

44. Hawe P, Shiell A, Riley T. Theorising interventions as events in systems. *Am J Community Psychol.* 2009;43(3-4):267–276.

45. Rickles D. Causality in complex interventions. *Med Health Care Philos.* 2009;12(1):77–90.

46. McGlashan TH. Duration of untreated psychosis in first-episode schizophrenia: marker or determinant of course? *Biol Psychiatry.* 1999;46(7):899–907.