Human pluripotent stem cells recurrently acquire and expand dominant negative P53 mutations

A community health worker program to treat depression in rural Mexico:

Analysis of a stepped-wedge program roll-out

Alyssa Bilinski,[1,2,3] Hector Carrasco,[1] Mercedes Aguerrebere,[1] Patrick M. Newman,[4] Daniel Palazuelos,[1,5,6] Richard Silverwood,[2] Molly F. Franke,[5] Patrick Elliott[1, 6]

[1] Compañeros En Salud, Angel Albino Corzo, Chiapas, Mexico and Partners In Health, Boston, MA, USA
[2] Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London, UK
[3] Harvard University Graduate School of Arts and Sciences, Interfaculty Initiative in Health Policy Cambridge, MA, USA
[4] Division of Hospital Medicine, Department of Pediatrics, University of California, San Francisco School of Medicine, San Francisco, CA, USA
[5] Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA
[6] Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA

Corresponding author: Alyssa Bilinski (abilinski@g.harvard.edu)

Abstract

Background

Depressive disorders are the second-leading cause of global disability, and an area of increasing focus in international health efforts. We describe a community health worker (CHW) program rolled out in a stepped-wedge design during the course of routine patient care to 74 patients with depression in 4 communities in rural Mexico.

Methods

We used random effects models to calculate the change in Patient Health Questionnaire-9 (PHQ-9) scores, an internationally validated measure of depression, before and after the CHW program was introduced. As a secondary outcome, we also examined the change pre- and post-intervention in the proportion of patients who had a mean of at least one visit per month for depression follow-up, in accordance with clinic visit guidelines.

Results

In multivariate mixed-effects regression, the introduction of the CHW program was associated with a 2.1-point decrease in PHQ-9 score (95% CI: -3.7 to -0.50) followed by a decrease in PHQ-9 score of 0.19 points per month (95% CI: -0.41 to 0.02), beyond standard care. There was strong evidence that patients were far more likely to attend a mean of at least one visit per month (adjusted OR = 8.5, 95% CI: 7.2 to 9.7) after the intervention was introduced in a community.

Conclusions

Our results suggest an association between the introduction of a CHW program and improved depression outcomes and appointment adherence. Our findings are limited by missing data. Future research is necessary to develop evidence-based mental health interventions implementable in low-resource settings.

Keywords

depression, CHW, community health, Mexico, LMIC

Background

Depressive disorders are the second-leading cause of global disability, responsible for 3% of disability-adjusted life years (DALYs) [1], and fewer than half of individuals suffering from depression globally receive any kind of treatment [2]. As awareness of the burden of mental health disorders in low- and middle-income countries (LMICs) has improved, there have been increasing calls to incorporate mental health care into international priorities [3] and to develop culturally-appropriate, scalable programs to address mental health problems in these regions [2].

Substantial evidence indicates that depression can be managed through anti-depressants and behavioral interventions, but the majority of the literature comes from high-income countries [4]. Studies from LMICs have generally found these interventions to be effective, but this body of evidence is limited relative to that of high-income areas [4–8]. For example, a randomized-controlled trial that evaluated a community-based depression intervention for low-income women in Chile found strong evidence that community-based care significantly decreased Hamilton depression rating scores, compared to those in traditional primary care [6]. Similarly, a cluster-randomized group therapy intervention in Uganda reduced depression severity significantly compared to controls [5]. However, such studies are relatively uncommon, limited in scope, and have not fully explored how depression interventions can be effectively integrated into routine care delivered through the primary health care system.

In Mexico, approximately 8% of the population experiences a major depressive episode in his or her lifetime according to the Mexico National Comorbidities Survey [9]. Mental health care is included as part of the essential package of cost-effective services included in Mexico's national health insurance *Seguro Popular* [9–11]. Still, access is limited with only an estimated

15% of individuals with mood disorders receiving minimally adequate treatment [12]. We found only one randomized-controlled trial from Mexico regarding depression, which focused on an education intervention in an urban area, Mexico City, and demonstrated limited effectiveness [4].

One intervention that has been proposed as part of the development of mental health services in LMICs is the provision of services by community health workers (CHWs). CHWs, local community members trained to provide decentralized services and psychosocial support, have played a key role in controlling infectious disease in developing countries, particularly HIV [13–16]. They have also been effective in assisting patients with mental illness in the US [17]. However, there is little evidence on role of CHWs in treating non-communicable diseases in resource-poor settings [18], and most evidence does not measure the effectiveness of CHWs to treat mental health conditions within the context of routine primary care.

In this paper, we analyze a stepped-wedge roll-out of community health workers to treat patients with depression in Chiapas, Mexico. We first describe the development and implementation of a decentralized mental health intervention utilized in rural setting. We then quantify the impact of the intervention, through measurement of PHQ-9 scores, a quantitative measure of depression, and change in patient visit patterns before and after the intervention.

Methods

Project background

Chiapas is Mexico's southernmost state, bordering Guatemala. More than half of the state's population lives below Mexico's poverty line [19], and the population has a high burden of chronic illness [20].

In 2011, Partners In Health (PIH), an international non-profit, launched a sister organization, Compañeros En Salud (CES), to support government-run health clinics in the

Sierra Madre region of Chiapas. In 2014, CES began an evaluation of the community health worker program for patients with chronic illnesses in 4 communities. Primary data collection only included patients with diabetes and hypertension, but routine illness data for all patients who received a CHW was concurrently collected in CES's electronic medical record. This article describes retrospective analysis based on depression data from electronic medical records.

Program introduction & CHW recruitment

The CHW program was rolled out in a stepped fashion approximately every 3 months during one year (from March through December 2014), and the order in which communities initiated the intervention was randomized (Figure 1). Each community held a public meeting to propose the program's introduction, during which program activities were described, and stakeholders had opportunities to share questions and concerns.

Following the initial meeting, nominations for CHWs were collected from community members and staff from the health center. Nominees were required to be female, aged 18-60, literate, and able to dedicate 5 hours per week to CHW duties. Following nomination, program representatives interviewed and selected 1 CHW per approximately 6 patients with chronic diseases.

Staff structure and training

CHWs received 32 hours of introductory training regarding the treatment of patients with chronic illnesses, including diabetes, hypertension, epilepsy, depression, and asthma. Of these, approximately 5 hours focused specifically on mental health topics including symptoms and physiology of depression, side effects of antidepressant medications, and techniques for communicating effectively with patients. Training emphasized role-play scenarios during which

CHWs could practice intervention techniques. Addition psychoeducation for CHWs was also provided over the course of the intervention.

Patient recruitment

Patients were diagnosed with depression by a community physician if they reported depressive symptoms for at least 2 weeks, as recorded in a PHQ-9 score or manually documented in a chart, meeting DSM V criteria for depression. Approximately 7.9% of patients in CES's catchment area met the formal criteria for depression [21]. All patients with depression who lived in a community with CHWs were eligible to receive a CHW. Patients with depression were offered a CHW when the program was introduced in their community, and after program introduction, new patients were offered a community health worker following diagnosis. Those who declined a CHW continued to receive standard care from the community physician.

CHW visit techniques

CHWs visited patients with depression once per week for 20-30 minutes, increasing or decreasing the frequency of patient visits per an individual patient's needs. If a patient was not home for a visit, the CHW returned until a patient became available. CHW support focused on 4 main tasks: encouraging patients to "name the problem"; providing hope that the illness was treatable; identifying and encouraging tasks that could help patients manage their illness; and mobilizing social support from friends and family.

Patient follow-up and monitoring

Patients with depression were also given monthly appointments with their community physician, during which progress was noted and Patient Health Questionnaire 9 (PHQ-9) score was documented in an electronic medical record. The PHQ-9 is designed to assist in the diagnosis and management of patients with depression in primary care and has been previously

validated in a wide variety of patient populations, including the study population [22–25]. Patients with a PHQ-9 score higher than 15 were offered selective serotonin reuptake inhibitors (SSRIs), either fluoxetine or sertraline.

Study design and population

We performed a retrospective cohort study of all patients who were referred to the CHW program for a diagnosis for depression between December 1, 2013, and June 31, 2015. We conducted a review of patient's medical charts to collect clinical and sociodemographic data prior to and following the implementation of the community health worker intervention.

Outcome variables

Our primary outcome was PHQ-9 score at routine visit, measured as a continuous variable. A higher PHQ-9 score indicates poorer depression control, with scores greater than 5 indicating mild depression and score greater than 10 indicating moderate depression [26].

Our secondary outcome was frequency of patient visits to the community physician, which were scheduled at least monthly. We analyzed this as a binary variable, by calculating the mean number of visits per month for each patient over the enrollment period: 1) during the pre-intervention period and 2) during the post-intervention period, and then created a variable equal to 1 if the mean number of monthly visits was ≥ 1 and 0 otherwise. Though the number of recommended visits per patient varied by disease severity, all patients should have received at least one visit per month.

Predictor variables

Individuals were considered exposed on the first day of program implementation in his/her community. To estimate an interaction between the CHW intervention and time exposed

to the intervention, we calculated time since the initiation of the CHW intervention, measured in months.

Covariates

We collected the following covariate data: age, sex, whether a patient had other chronic illnesses in addition to depression that would render her eligible for a CHW, whether a patient had ever been prescribed antidepressant medication, and time in months since a patient's diagnosis with depression.

Descriptive analyses

In descriptive analyses, we tabulated demographic and baseline clinical statistics of patients overall and in each community. We also calculated the percentage of visits missing a PHQ-9 score, our primary outcome measure. We graphed patient trajectories, both overall and by community, in order to visualize PHQ-9 score trends over time.

Regression analyses

We used linear mixed-effects regression to estimate patient PHQ-9 scores over time at the visit-level, including random intercepts at the patient and community level. Our unadjusted model included PHQ-9 score vs. time since intervention and time since diagnosis. We then conducted a second adjusted analysis which included dummy variables for age groups, sex, whether the patient had a prescription for anti-depressants, and whether the patient was diagnosed with another chronic illness besides depression. We third added a term to consider the possibility of different slopes in patient trajectory, a random slope associated with time since intervention). For our secondary outcome, we used logistic mixed-effects regression to estimate the odds ratios associated with attending a mean of at least 1 visit per month, with random intercepts at the patient and community level. As we had a small sample size, we chose to use

restricted maximum likelihood for model estimation. We used AIC, which incorporates both log-likelihood and number of parameters to provide a measure of model quality.

All analyses were conducted in R 3.1.2. Ethics approval was obtained from the Partners Healthcare IRB (Protocol # 2015P001387/BWH).

Results

Descriptive statistics

Our sample contained 74 patients who attended 802 visits during the study period (**Figure 2)**. Mean patient age at first visit was 38, and 63 patients (85%) were female. Sixty-three patients (85%) were prescribed antidepressants at some point during the study period. Nearly a fifth of patients (n = 14, 19%) were diagnosed with at least one additional chronic illness in addition to depression.

The mean baseline PHQ-9 score was 13.6, which indicates moderate to severe depression. However, the baseline PHQ-9 score was only available at a patient's first visit in 43% of patients (n = 32); in the remaining patients, it was calculated based on the first measured PHQ-9 score. Overall, 60% (n=479/802) of visits had PHQ-9 score data; not every visit required a PHQ-9 score.

As the timing of the intervention was determined community level, we compared communities based on demographic and baseline clinical variables. Though we observed some heterogeneity between communities, they were similar in terms of most variables we measured, including age at diagnosis, percentage female, and baseline PHQ-9 score. We did, however, observe some differences. In particular, the percentage of patients with a chronic illness was higher in Community A (44%, n/N = 7/16) than the sample average (19%, n/N = 14/74).

253 ***Primary Outcome: PHQ-9 Score***

254 Overall, PHQ-9 score decreased over time (**Figure 3**). Results from primary analyses are
255 displayed in **Table 1**. Our unadjusted model predicted PHQ-9 score decreased by 1.7 (95% CI: -
256 3.3 to -0.08) points immediately following the intervention, and by 0.18 points each month
257 thereafter (95% CI: -0.40 to -.04). After the minimum 9 months of follow-up, the model
258 predicted a 3.3-point decrease in PHQ-9 score (95% CI: -5.7 to -0.96).

259
260 ***Table 1. Linear mixed effects regression of PHQ-9 score on CHW intervention.*** Models #1 -
261 #3 contain random intercepts by patient and community while model #3 also contains a random
262 slope on time since intervention.
263

	Dependent variable:		
	PHQ-9 score		
	(1) Unadjusted	(2) Adjusted	(3) Adjusted + RS
Intervention	-1.69**	-2.09**	-2.11**
	(-3.30, -0.08)	(-3.68, -0.50)	(-3.78, -0.43)
Time since intervention (months)	-0.18	-0.19*	-0.22*
	(-0.40, 0.04)	(-0.41, 0.02)	(-0.45, 0.02)
Time since diagnosis (months)	-0.23***	-0.21***	-0.22***
	(-0.40, -0.07)	(-0.37, -0.06)	(-0.38, -0.06)
Age 30-39		-1.05	-1.08
		(-3.86, 1.76)	(-3.94, 1.78)
Age 40-49		-3.40**	-3.74**
		(-6.62, -0.19)	(-7.00, -0.47)
Age 50+		-3.74**	-3.85**
		(-6.78, -0.69)	(-7.00, -0.70)

Sex		-3.42**	-2.98*
		(-6.50, -0.33)	(-6.20, 0.24)
Other chronic illness		-1.77	-1.15
		(-4.85, 1.31)	(-4.30, 2.00)
On antidepressants		-3.18*	-2.99*
		(-6.68, 0.33)	(-6.51, 0.53)
Constant	12.55***	21.45***	20.99***
	(11.06, 14.05)	(16.15, 26.74)	(15.55, 26.43)
Observations	479	478	478
Log Likelihood	-1,528.91	-1,504.73	-1,503.04
Akaike Inf. Crit.	3,071.83	3,035.47	3,040.08
Bayesian Inf. Crit.	3,101.03	3,089.67	3,110.97
Note:			*p<0.1; **p<0.05; ***p<0.01

In the adjusted model (2), the point estimate for the immediate effect of the intervention was slightly larger (-2.1 points, 95% CI: -3.7 to -0.50), and the strength of the evidence for the time since intervention effect remained similar (-0.19 points/month, 95% CI: -0.41 to 0.02). After 9 months of follow-up, the model predicted a 3.8-point decrease in PHQ-9 score (95% CI: -6.1 to -1.5).

In model (3), we added a random slope for on time since intervention to the adjusted model. The point estimates for the intervention effects remained similar (-4.1 points after 9 months, 95% CI: -6.5 to -1.7).

The AIC for model (2) was substantially lower than the AIC for model (1), suggesting that adjusting for additional variables helped us to better explain the data. However, the AIC for models (2) and (3) were virtually identical, indicating similar fit.

Secondary Outcome: Mean Visits Per Month

Results from our secondary analysis, which explored the change in mean number of visits per month before and after the intervention, are displayed in **Table 2**. In unadjusted analysis, there was strong evidence that the odds of having ≥ 1 visit per month on average were greater after the introduction of the intervention (OR: 7.8, 95% CI: 6.4 to 9.1). This effect larger in adjusted analysis, with an odds ratio of 8.5 (95% CI: 7.2 to 9.7) comparing the pre-intervention to post-intervention period.

Table 2. Logistic mixed effects regression of mean visits per month on CHW intervention. Both models contain random intercepts at the patient and community levels.

	Dependent variable:	
	Binary: avg ≥1 visit/month	
	(1) Unadjusted	(2) Adjusted
Intervention	7.76***	8.47***
	(6.44, 9.07)	(7.23, 9.72)
Time since diagnosis (months)	0.99***	0.97***
	(0.88, 1.11)	(0.86, 1.08)
Age 30-39		0.60
		(-0.55, 1.76)
Age 40-49		0.97
		(-0.32, 2.25)

Age 50+		0.87
		(-0.33, 2.06)
Sex		1.51**
		(0.28, 2.74)
Other chronic illness		3.12***
		(1.85, 4.39)
On antidepressants		6.93***
		(5.46, 8.40)
Constant	0.45	0.06
	(-0.35, 1.26)	(-2.35, 2.46)
Observations	140	139
Log Likelihood	-85.13	-77.49
Akaike Inf. Crit.	180.27	176.97
Bayesian Inf. Crit.	194.98	209.25
Note:	*p<0.1; **p<0.05; ***p<0.01	

Discussion

Our analysis of clinical data collected during a CHW intervention suggests the intervention was associated with improved depression symptoms and more patient visits. During the minimum 9-month post-intervention follow-up period, this translates to a 3.8 decrease in PHQ-9 score beyond that which was achieved by standard care. PHQ-9 score has been found to "broadly reflect" depression severity over time [23, 27], and a higher patient PHQ-9 score has been correlated with negative health outcomes in this patient population [22]. In our model, CHW effect size was larger in magnitude than the effect of being prescribed antidepressants, a

297 3.2-point decrease. It was also larger in size than effect of "time since diagnosis", a variable
298 intended to capture the effect of routine care outside of CHW support, roughly a 3-point decline
299 over the average 15 months of time since diagnosis.
300 We further found that the mean number of patient visits per month increased following
301 the introduction of the CHW program, with the odds of a patient attending a mean of at least one
302 visit per month in the post-intervention period about 8 times higher than in the pre-intervention
303 period. This suggests that patients had more regular contact with physicians following the
304 intervention, possibly a result of CHWs improving adherence to clinical visits.
305 This study aims to address a dearth of literature describing culturally appropriate mental
306 health interventions that are implementable in low-resource settings [2]. The CHW program
307 described in this report relies on trained local community members to support facility-based care
308 provided by primary care physicians (PCPs). Some mental health interventions, such as the
309 WHO-CHOICE's recommended "proactive collaborative care" in developing regions, aim to
310 support PCPs by including psychologists and psychiatrists in the provision of mental health care
311 in developing countries [11, 28, 29]. However, such interventions have rarely been tested in
312 resource-poor countries [28, 29], and relying on specialized mental health professionals is often
313 infeasible. For example, there are currently 26 psychiatrists in the state of Chiapas, which has a
314 population of 4.8 million [30]. Task-shifting to less specialized health professionals has been an
315 effective way to scale up treatment for other illnesses [31], and may assist in managing the
316 growing burden of depressive and mental illness.
317 Though we observed an association between the CHW program and our outcomes, we
318 are limited in our ability to draw casual claims about the relationship between the program and
319 patient depression. During the course of the CHW roll-out, there were ongoing efforts being

performed to improve the quality of care, both overall and targeted toward patients with depression at CES. We were unable to quantify these factors in our analysis, but they may have impacted PHQ-9 scores and trends and may have contributed to a greater number of patient visits to the clinic. We cannot eliminate the possibility that other interventions accounted for all or part of our observed treatment effect or for the interaction between treatment and time. However, the stepped-wedge design helps to address secular trends: PHQ-9 score decreased fairly quickly following the introduction of CHW programs at different times in different communities.

Figure 3 also shows a wide variety of pathways patients took when working towards clinical improvement. Such variability likely represents an important challenge, and opportunity, for titrating CHW interventions to specific patient needs. This is especially true if these fluctuations are related to social-economic conditions that peer-CHWs are arguably best equipped to recognize and understand, such as crop failures or political turmoil.

We were also only able to measure the intervention at the community level rather than the patient level. It is therefore possible that some patients were considered as having received the intervention when they had not yet initiated; however, we suspect that this misclassification would have attenuated the association between the intervention and our outcomes and therefore is not a source of bias that could explain our findings. In addition, our work may not generalize to all clinic populations. In particular, CES conducts door-to-door screening for depression in their communities, which may result in diagnosis of depression and engagement in care of patients who otherwise would not have sought care on their own. Finally, missing PHQ-9 score data may bias our results. As not every visit required a PHQ-9 score, it was difficult to assess potential effects of missing data.

Future work might explore which types of CHW-led interventions most improve depression symptoms. Several mechanisms may have contributed to program effect including: improved understanding of their disease (informational support), improved feelings of social wellbeing and social connectedness with regular home visits (emotional support), increased family intervention in the patient's care, improved adherence to prescribed SSRIs (motivational support), and improved patient activation for participation in psych-medical advice given (instrumental support and peer-coaching). Future research can help delineate the relative strength of these mechanisms in order to better design effective CHW-led interventions. It would likewise be useful to compare different packages of depression interventions and quantify the cost and value of these interventions.

Conclusions

Community health workers have been widely deployed to address a range of public health problems and may be able to improve depression outcomes. Our study provides evidence that a community-based depression program integrated into primary care in a rural setting was associated with improved outcomes. Future research might more rigorously explore the relationship between such programs and outcomes and the best way to deploy such programs.

List of abbreviations

CHW, community health worker; PHQ-9, Patient Health Questionnaire-9; DALY, disability adjusted life years; LMIC, low- and middle-income countries; PIH, Partners In Health; CES, Compañeros en Salud; SSRIs, selective serotonin reuptake inhibitors; PCPs, primary care physicians

Declarations

- **Ethics:** Ethics approval was obtained from the Partners Healthcare IRB (Protocol # 2015P001387/BWH).
- **Consent for publication:** NA
- **Availability of data and material:** Data is available from CES for researchers who meet requirements for working with patient records. Contact LPalazuelos@pih.org.
- **Competing interests:** The authors declare that they have no competing interests.

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- **Authors' contributions:** AB, HC, MA, PN, PE, MF designed the study. AB, MF conducted analyses. AB wrote the first draft. All authors edited the draft and approved the final manuscript.
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Figure Titles

Figure 1. Study schematic. During control periods (grey), CHWs were not provided to chronic disease patients; during intervention periods (black), they were provided.

Figure 2. Demographic and baseline clinical variables by community. The dashed grey line indicates the overall inter-community mean for the variable. The black bars indicate the 95% confidence interval for the variable.

Figure 3. Patient trajectories. The light purple dots and lines in the background indicate trajectories of individual patients. The solid black line is the LOWESS smoother of all patient trajectories, and the grey band surrounding it is the 95% confidence interval. The dotted purple line indicates the date at which CHWs were introduced into a community.

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