

# How effective is antidepressant medication polypharmacy in difficult-to-treat depression? A NeuroBlu Electronic Health Record report

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## BACKGROUND

Difficult-to-treat depression (DTD) is defined as “depression that continues to cause significant burden despite usual treatment efforts”.<sup>1</sup> Antidepressant medication (ADM) polypharmacy is a strategy of administering multiple antidepressants with different mechanisms of action with the goal of maximising treatment efficiency, moderate side-effects, and treat a broad range of symptoms.<sup>2,3</sup>


## OBJECTIVE

- To identify the proportion of DTD patients that receive varying degrees of ADM polypharmacy.
- To assess outcomes of disease severity using the Clinical Global Impression Scale (CGI-S) and daily function using the Global Assessment of Function (GAF) associated with each level of ADM polypharmacy.
- To compare those with meaningful gains and losses (+/-) of benefit over 6 months.

## METHOD

- A retrospective cohort study was conducted on adults (18 years and older) with DTD in the NeuroBlu dataset who had an outpatient visit, CGI-S score, and GAF recorded within +/-14 days of 3 measurement occasions (0, 3, and 6 months).
- Patient cohorts were defined by the number of distinct ADMs (#0-4+) prescribed during the 6-month observation period, this was not limited to new prescriptions.
- Descriptive statistics and chi-squared tests were used to evaluate the relationships between baseline demographics, ADMs, and psychiatric comorbidities with outcomes.
- Outcomes (+/-/no change of CGI-S score/GAF) were calculated using linear regression.

## NeuroBlu™ database






 **50+ million** Rows of patient data  
**560K+** Patients  
**20+ years** Longitudinal data

### Patient volume by disease



153K Substance-related Disorders	68k Bipolar Disorders	63k Adjustment Disorders	54k ADHD
46k PTSD	29k Personality Disorders	24k Conduct Disorders	
129K Major Depressive Disorder	43k Generalized Anxiety Disorder	15k Panic Disorder	15k Schizophrenia

Figure 1. NeuroBlu Database overview

### Structured Data

-  Outcome Measures (e.g., CGI-S scores, GAF levels)
-  Diagnosis Codes (ICD-9, ICD-10)
-  Prescription Data
-  Patient Demographics
-  Emergency department, inpatient, and outpatient data across the same patients in 20 of 25 clinics

### Unstructured Data

-  Mental Status Examination (MSE)
  - Categorized notes on patient's function, appearance, and mood at a visit
  - Holmusk developed >30 advanced Neural Network models to predict structured labels from MSE
  - Created >300 psychiatry specific labels in collaboration with clinicians to track disease progression over time
-  External Stressors  
Social, relational, and occupational events that may affect the patient's mental health

## Data Source of US Health Facilities

De-identified EHR data were obtained from U.S. mental health services that use the MindLinc EHR system. The data were analysed in NeuroBlu, a secure Trusted Research Environment (TRE) that enables data assembly and analysis using an R/Python code engine.

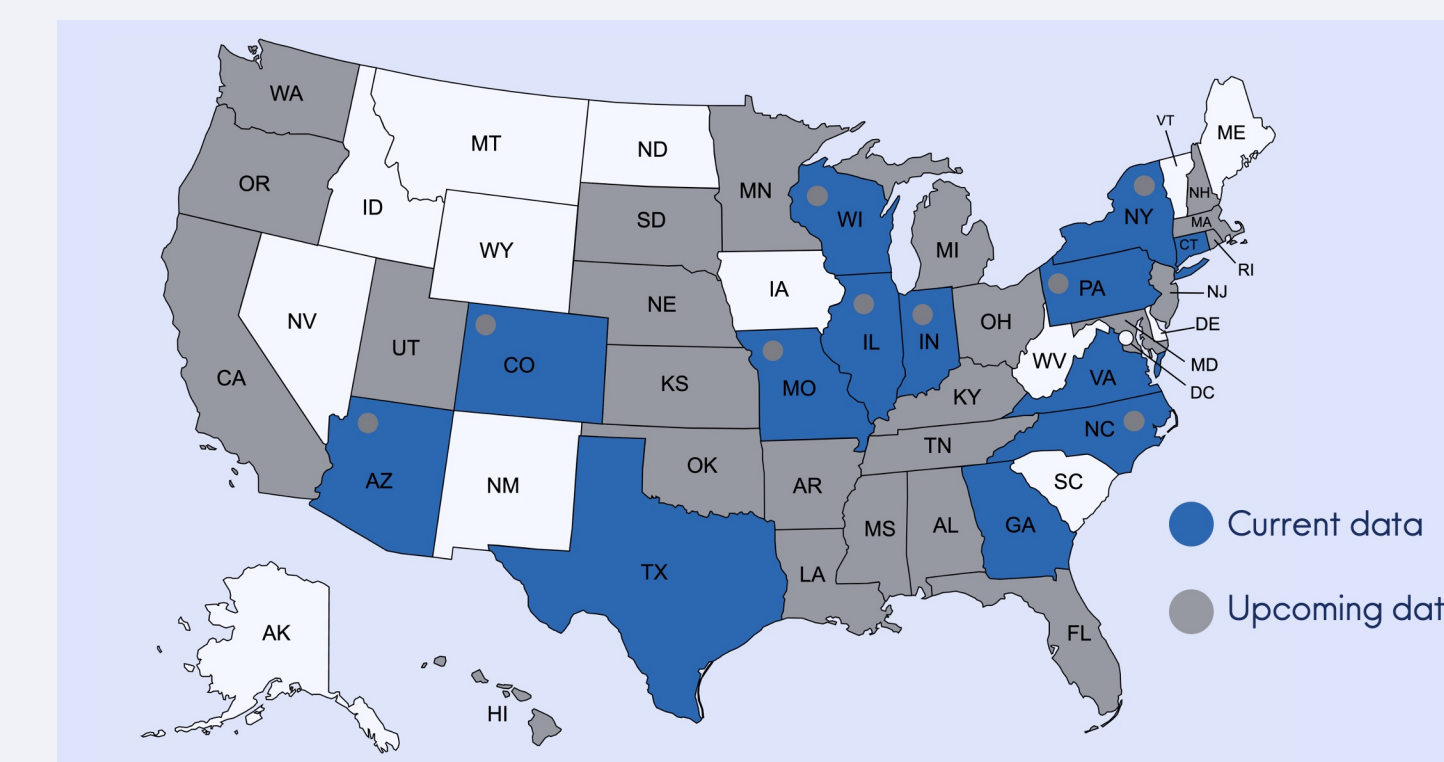
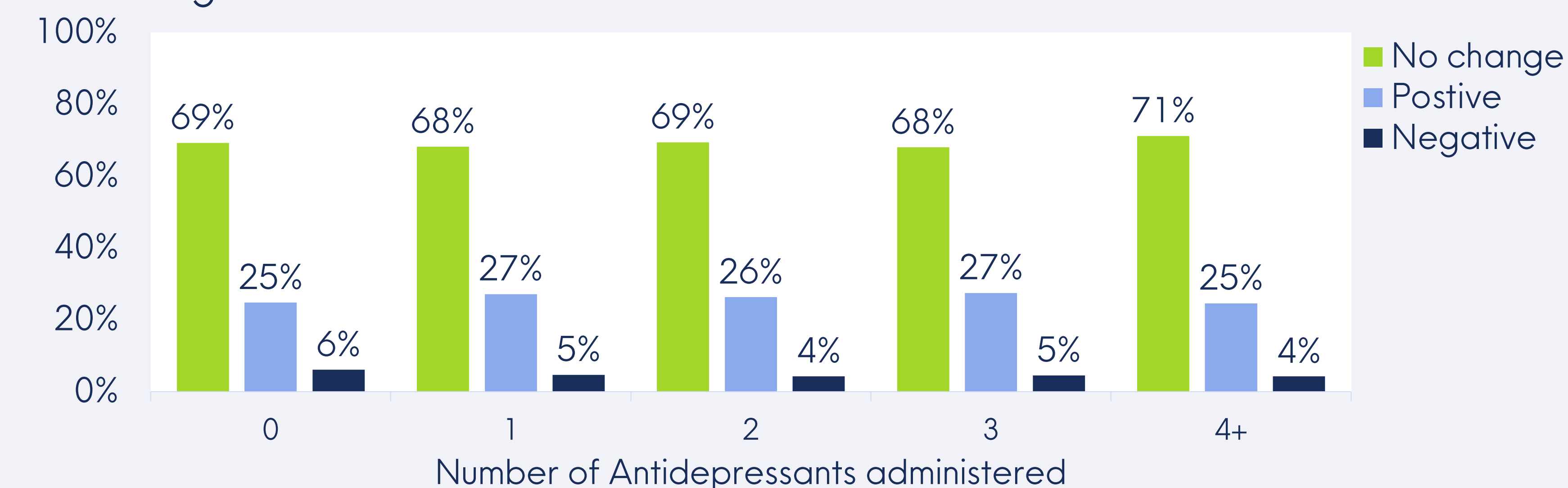


Figure 2. State-specific data source for NeuroBlu

## RESULTS

Altogether, 3,659 DTD patients (mean age= 43.5 [SD=14.0] years; 26.6% male) received 0, 1, 2, 3, or 4+ ADMs (21%; 38%; 28%; 10% and 3% respectively). Baseline mean CGI-S score and GAF levels were 4.16 (0.96) and 55.0 (10.4), respectively (Table 1). The CGI-S score ( $\chi^2 = 5.06, p = 0.75$ , Figure 3A) and GAF ( $\chi^2 = 5.24, p = 0.73$ , Figure 3B) groupings based on +/-/no change were unrelated to the number of ADMs prescribed, but based on each measure, these outcome groups were significantly related to each other ( $\chi^2 = 226.62, p < 0.001$ ).

### A. Change in CGI-S score over 6 months



### B. Change in GAF levels over 6 Months

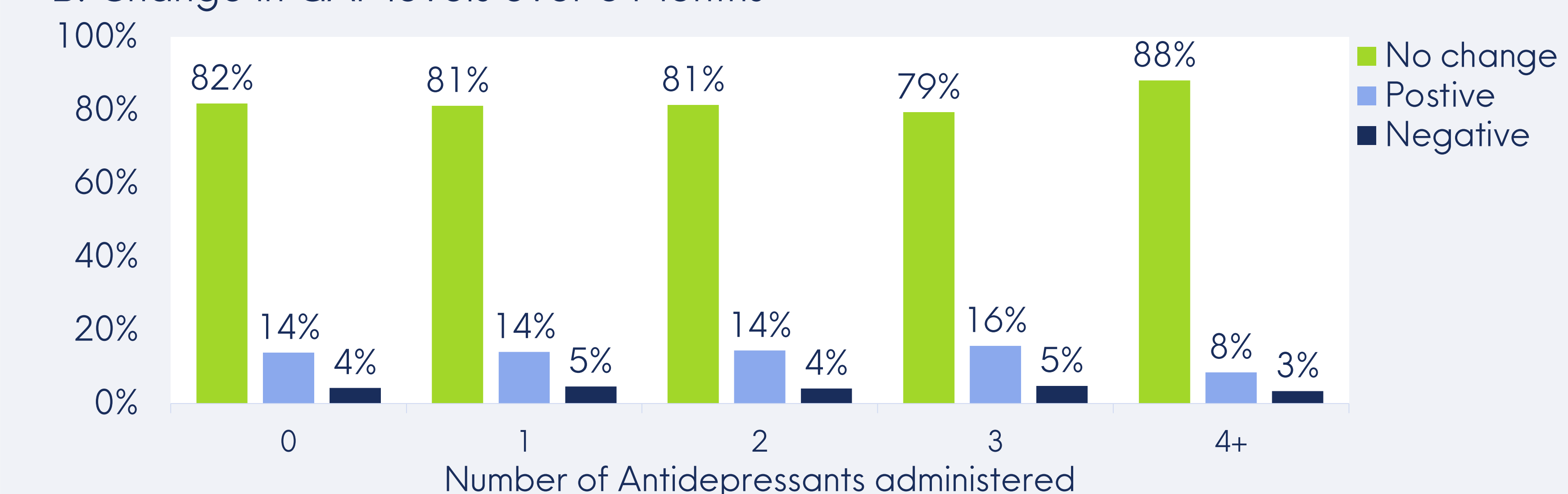


Figure 3. Proportion of patients with difficult-to-treat depression (n=3,659) that had a positive (light blue), negative (dark blue), or no change (green) in their CGI-S (A) or GAF (B) score over a 6-month period, grouped by number of antidepressants the patients received.

Table 1. Baseline characteristics of patients with difficult-to-treat depression (n=3,659) by antidepressant medication polypharmacy group

Number ADMs	N (%)	Age Mean (SD)	Gender Male (%)	Race White (%)	CGI-S Mean (SD)	GAF Mean (SD)
0	773 (21.13)	39.85(13.96)	24.32%	67.27%	4.34 (0.92)	51.85 (9.61)
1	1389 (37.96)	44.31 (14.44)	27.29%	51.84%	4.02 (0.99)	56.42 (10.52)
2	1004 (27.44)	45.06 (13.65)	28.59%	57.57%	4.15 (0.99)	55.70 (10.71)
3	375 (10.25)	44.11 (13.61)	24.00%	58.93%	4.24 (0.89)	54.74 (10.44)
4+	118 (3.22)	43.03 (14.11)	25.42%	54.24%	4.34 (0.85)	52.69 (10.03)

## CONCLUSION

Most DTD patients had little improvement in severity or function. Interestingly a large proportion of patients (21%) had no antidepressant prescribed at all during the six-month observation period. A higher number of ADM prescriptions was not associated with better outcomes. This is in line with a previous longitudinal study, which included 195 patients with depressive disorders and found no benefit of polypharmacy over monotherapy.<sup>4</sup> A limitation of the present study is that the side effects of treatment were not recorded. Concerns about drug interactions leading to increased side effects are often a barrier to the use of antidepressant polypharmacy. Despite this, due to the different mechanisms of action, polypharmacy can result in fewer side effects than other approaches, such as increasing doses.<sup>2</sup> Future investigations may wish to investigate the effect of polypharmacy on specific symptom severity reduction and overall patient wellbeing.

**Conflicts of Interest:** All authors report current employment with Holmusk Technologies, Inc. MV, AJR and SK report equity ownership in Holmusk Technologies, Inc.

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