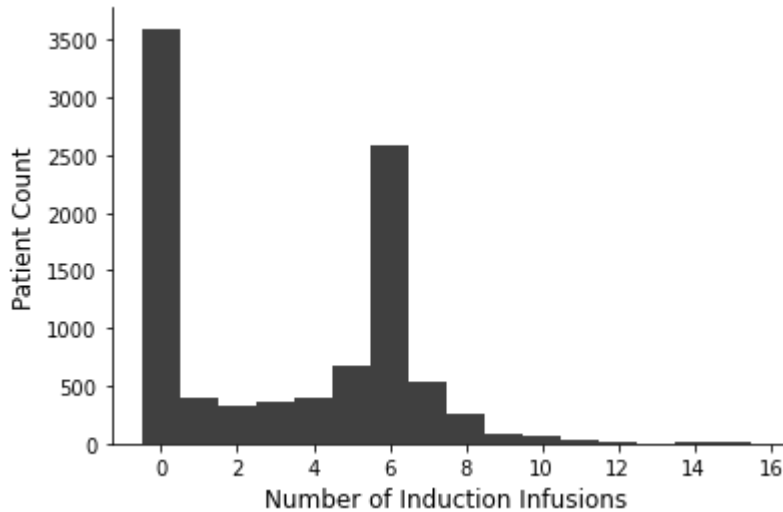
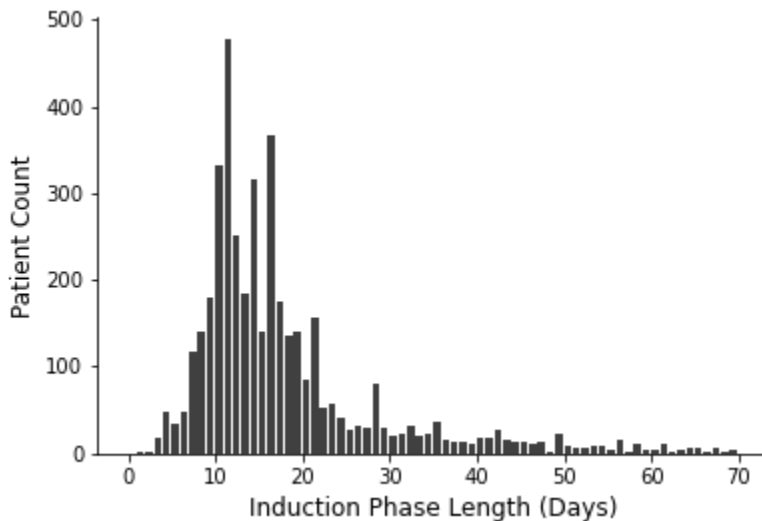


Supplementary materials

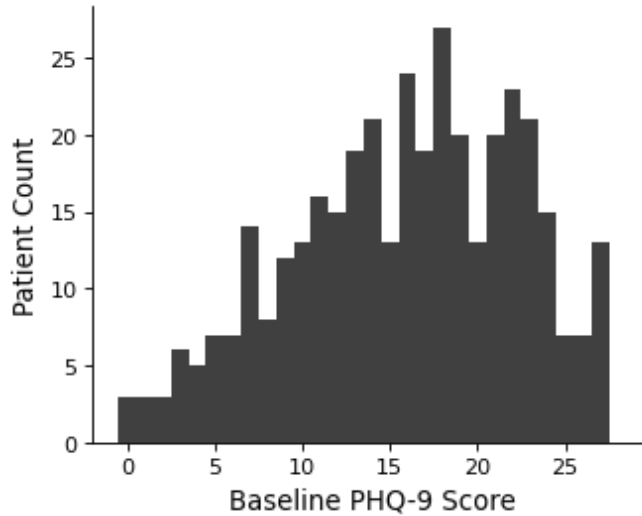
Supplementary Figures



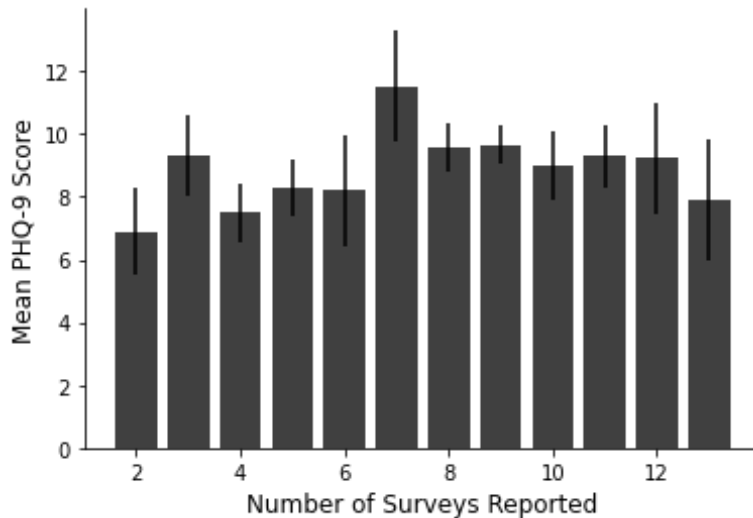
Supplementary Figure 1: the distribution of the number of induction infusions for all 9016 depression patients, without applying any screening criteria. The large number of patients with 0 induction infusions reflects the practice of clinics that used the software for mood tracking / patient-reported outcomes, while logging treatment data in a separate system and therefore not reporting treatment dates or parameters. A small number of patients had over 10 treatments marked as part of the initial series. The designation as an induction treatment is a feature of the software, permitting clinicians to denote each infusion as induction or maintenance. It is possible that clinics who marked patients with a large number of induction infusions incorrectly designated the infusion type. The most common protocol is for patients to receive 6 induction infusions. Some patients receive 7-8 induction infusions, and a sizable subset of individuals receive single infusions or 2-5 infusions.



Supplementary Figure 2: the distribution of induction length for all patients receiving 4-8 infusions. There is variance in the time period of induction treatments and in the community, and treatment schedules are often dictated by convenience or other nonclinical factors. The mean and SD length of the induction phase was 17.6 days \pm 11.2 days (median was 14.0 days). The figure shows a peak at 12 days.

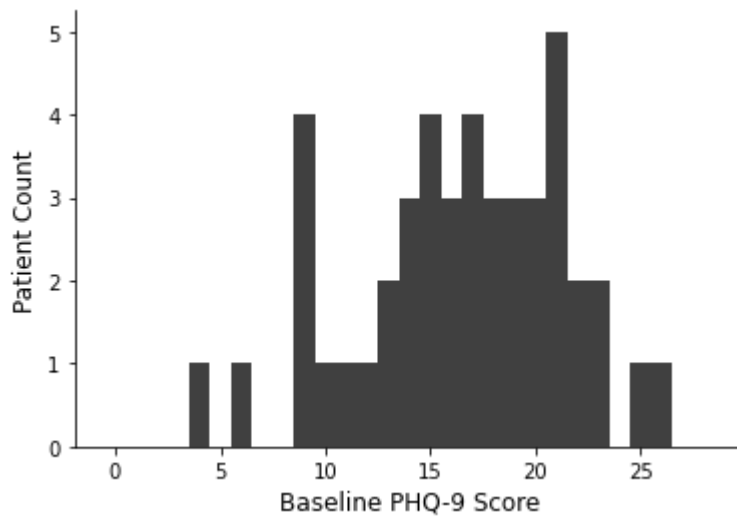


Supplementary Figure 3: the distribution of all available baseline PHQ-9 scores (n=374) for individuals who stopped receiving infusions before completing the induction. The mean and SD was 15.9 \pm 6.4.

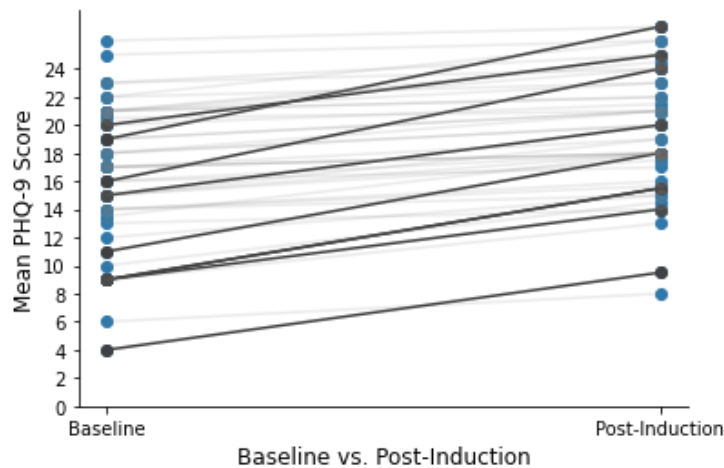


Supplementary Figure 4: the mean PHQ-9 scores 14-31 days after induction infusion 6, grouped by the number of questionnaires completed by patients, for the 381 patients who got 6 induction infusions. Error bars represent one standard deviation. The cohort sizes displayed, respectively, are 19, 25, 27, 23, 11, 17, 81, 101, 35, 22, 9, and 4. The figure does not display outliers: 2 patients reported 14 surveys, 2 patients reported 15, 2 patients reported 16, and 1

patient reported 20 surveys. There was no statistical relationship between the mean PHQ-9 score and the number of surveys reported ($\chi^2(26) = 253.0, p > 0.99$).

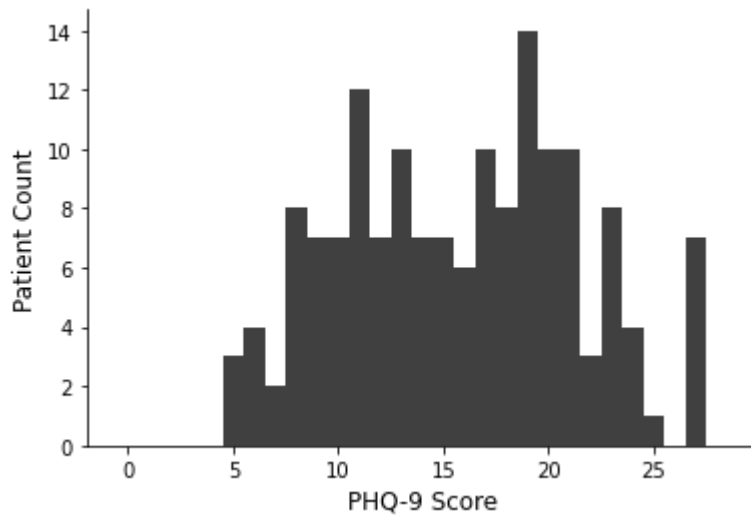


Supplementary Figure 5: the baseline PHQ-9 score distribution for the 45/537 patients who experienced an increase in PHQ-9 score during induction. The mean baseline PHQ-9 for this cohort was 16.5 ± 4.97 .

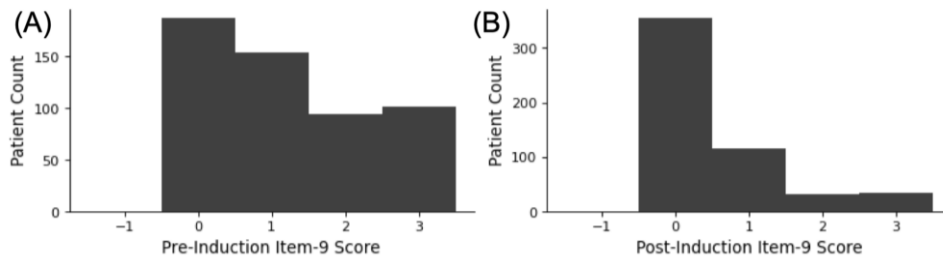


Supplementary Figure 6: PHQ-9 score before and after for the 45/537 patients who experienced an increase in PHQ-9 score during induction. Patients who had a PHQ-9 score increase of < 5 are represented with blue markers and light gray lines. Patients who had an increase of ≥ 5 are shown with dark black markers and lines. Nine patients experienced a score increase of ≥ 5 . For these 9 patients, the largest score increases were from two patients who changed from 19 to 27 and from 16 to 24. Six patients who were in the none/mild depression category at baseline worsened, with a baseline average PHQ-9 score of 7.7 and post-induction

average of 12.6. Eight patients who were in the moderate depression category at baseline worsened, with a baseline average PHQ-9 score of 12.7 and post-induction average of 15.8. Seventeen patients who were in the moderate-severe depression category at baseline worsened, with a baseline average PHQ-9 score of 16.9 and post-induction average of 19.8. Fourteen patients who were in the severe depression category at baseline worsened, with a baseline average PHQ-9 score of 21.9 and post-induction average of 23.9.



Supplementary Figure 7: the baseline PHQ-9 scores for the n=155 remitters. The mean and SD was 15.8 ± 5.6 . The numbers of remitters who started out in each level of depression (none/mild, moderate, moderately severe, severe) were 24, 43, 45, 43, respectively. The total numbers of patients within the n=537 cohort in each of these four categories were 41, 98, 157, 241, respectively. The likelihood of remission for each level of baseline depression was 58.5% (24/41), 43.9% (43/98), 28.7% (45/157), 17.8% (43/241). One of the 155 remitters did not achieve response as their PHQ-9 score dropped from 6 to 4.



Supplementary Figure 8: the distributions of SI (PHQ-9 line item 9 scores) at baseline and after induction. (A) The distribution of baseline item 9 scores for the n=537 cohort. (B) The distribution of post-induction item 9 scores for the n=537 cohort.

Number of induction infusions	Cohort size	Response rate	Mean PHQ-9 score decrease	Mean PHQ-9 score percent decrease	Median PHQ-9 score percent decrease
1	29	27.6%	2.9 (SD=5.4, 95% CI=0.8-4.9)	21.9% (SD=40.7%, 95% CI=6.8-37.0%)	25.0%
2	21	42.9%	6.1 (SD=4.6, 95% CI=4.1-8.1)	39.3% (SD=33.7%, 95% CI=24.5-54.0%)	41.7%
3	16	50.0%	7.2 (SD=5.7, 95% CI=4.3-10.1)	39.9% (SD=28.8%, 95% CI=25.3-54.5%)	46.2%
4	30	46.7%	7.4 (SD=6.3, 95% CI=5.1-9.7)	43.2% (SD=33.4%, 95% CI=31.0-55.3%)	47.9%
5	71	60.6%	9.0 (SD=6.9, 95% CI=7.4-10.6)	49.0% (SD=40.8%, 95% CI=39.4-58.6%)	54.5%
6	381	55.1%	8.9 (SD=6.4, 95% CI=8.3-9.6)	48.7% (SD=32.1%, 95% CI=45.5-51.9%)	53.8%
7	41	36.6%	6.6 (SD=7.1, 95% CI=4.4-8.8)	35.5% (SD=39.3%, 95% CI=23.3-47.7%)	29.4%
8	14	42.9%	8.5 (SD=8.4, 95% CI=3.9-13.1)	34.7% (SD=44.4%, 95% CI=10.6-58.9%)	41.8%

Supplementary Table 1: Outcomes as a function of the number of induction infusions. This analysis includes patients who had a single induction infusion, 2-3 induction infusions within 14 days, or 4-8 induction infusions over 7-28 days. Additionally, patients were required to have at least one PHQ-9 reported up to 4 weeks pre-induction and at least one PHQ-9 reported 14-31 days after their final induction infusion prior to any maintenance sessions. Multiple infusions are associated with a higher percentage response compared to a single infusion. However, the response rate falls off when 7 or 8 infusions are administered in the induction period.

Outcome	Value and comments
Number of maintenance infusions for all 3518 patients who completed KIT induction (regardless	Mean=2.6±5.0

<p>whether they reported sufficient PHQ-9 scores to be included in the n=537 cohort)</p>	<p>A subset of the patients in this analysis may still be receiving maintenance infusions so these numbers are not limited to patients who have already discontinued during the maintenance phase. The highest was 56 infusions.</p> <p>Many patients received few or no maintenance treatments, with a long tail for outliers (these high numbers might imply that those patients have received therapeutic benefit from ketamine infusions and are in long-term maintenance). A majority (52.5%) of patients who completed induction entered maintenance treatment.</p>
<p>Number of maintenance infusions received by the 288/537 patients who achieved response after induction</p>	<p>Mean=3.7 ± 5.0</p>
<p>Number of maintenance infusions received by the 155/537 patients who achieved remission after induction</p>	<p>Mean=3.6 ± 4.9</p>
<p>Time length between the final induction infusion and the first maintenance infusion for the 1846 patients who completed induction and entered maintenance</p>	<p>Mean=46.3 ± 89.1 days (median=28)</p>
<p>Time between consecutive maintenance sessions for the 1309 patients who completed induction and received at least two maintenance infusions</p>	<p>Mean=40.0 ± 55.4 days (median=28)</p>
<p>Time length between the final induction infusion and the first maintenance infusion for the 202 patients who completed induction, achieved response, and entered maintenance</p>	<p>Mean=75.1 ± 87.3 days (median=43)</p>
<p>Time length between two consecutive maintenance infusions for the 155 patients who completed induction, achieved response, and received at least two maintenance infusions</p>	<p>Mean=46.4 ± 61.3 days (median=33)</p>

Time length between the final induction infusion and the first maintenance infusion for the 109 patients who completed induction, entered remission, and entered maintenance	Mean=84.3 ± 93.9 days (median=48)
Time length between two consecutive maintenance infusions for the 81 patients who completed induction, entered remission, and received at least two maintenance infusions	Mean=47.5 ± 60.6 days (median=35)

Supplementary Table 2: Practice patterns for maintenance KIT.

Maintenance infusion number	Mean number of days between the end of induction and each maintenance infusion	Number of patients
1	88.6 (SD=100.1, 95% CI = 69.4-170.7)	108
2	143.5 (SD=124.5, 95% CI = 116.1-171.0)	80
3	183.7 (SD=145.5, 95% CI = 145.5-221.8)	57
4	228.9 (SD=148.4, 95% CI = 187.0-270.9)	49
5	243.1 (SD=142.1, 95% CI = 197.9-288.2)	39
6	271.9 (SD=131.2, 95% CI = 227.1-316.6)	34
7	287.6 (SD=246.2, 95% CI = 246.2-328.9)	31
8	350.1 (SD=171.3, 95% CI=286.6-413.6)	29
9	366.3 (SD=163.3, 95% CI=301.0-431.7)	25

Supplementary Table 3 shows the observed mean amount of time after the end of induction that each maintenance treatment was received, among the 108 remitters who met the criteria for response and had at least 1 maintenance infusion.

Number of days since the end of induction	Mean PHQ-9 score	Number of scores reported
14-28	3.2 (SD=3.0, 95% CI=2.7-3.7)	172
28-42	3.5 (SD=3.3, 95% CI=2.9-4.0)	141
42-56	4.2 (SD=3.4, 95% CI=3.6-4.8)	121
56-70	4.4 (SD=3.8, 95% CI=3.7-5.1)	119
70-84	5.5 (SD=3.8, 95% CI=4.7-6.3)	93

84-98	5.8 (SD=5.4, 95% CI=4.6-6.9)	90
98-112	5.8 (SD=5.6, 95% CI=4.6-7.0)	80

Supplementary Table 4 shows the observed mean PHQ-9 score throughout maintenance KIT for the 154 remitters who met the criteria for response. Patients could report multiple scores within each time period.