Early Remission is Associated with Lower Risk of Relapse: Analysis of Major Depressive Disorder using STAR*D

#CO200

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Introduction

- Major depressive disorder (MDD) is a serious and prevalent mental health disorder. A 2021 survey of US adults aged ≥18 years estimated 21 million people (8.3%) experienced ≥1 major depressive episode in the past 12 months.[1]
- Patients with MDD may have impairment in daily functioning and a decreased quality of life.[2]
- The standard pharmacological treatment for MDD over the past 60 years has been monoamine-based antidepressants,[3] which typically require several weeks to begin to take effect.[4,5]
- Prior studies have suggested an association between time-to-response and outcomes in MDD treatment. For example, the delay in the resolution of an MDD episode has been associated with an increased risk of relapse.[4,6-9] Therefore, patients with MDD who experience shorter durations of MDD episodes may have better symptomatic and functional outcomes.[6,10]

Objective

- To assess the impact of speed of remission (defined as a self-reported Quick Inventory of Depressive Symptomatology [QIDS-SR16] score of ≤5 sustained until the end of any treatment step) on time to relapse of MDD symptoms in the STAR*D trial (NCT00021528).

Methods

- Data from the STAR*D trial were used for this study. The STAR*D trial followed patients with MDD who received antidepressants as the first treatment step in an outpatient setting.[4] Patients who did not achieve remission were encouraged to proceed to the next treatment step, and patients who achieved remission entered a 12-month naturalist follow-up phase.[4]
- The study population consisted of all patients who achieved remission in the STAR*D trial, defined as a self-reported Quick Inventory of Depressive Symptomatology (QIDS-SR_{16}) score of ≤5 sustained until the end of any treatment step (ie, line of therapy).
  - Initiating a new treatment and/or adjusting the current treatment constituted a new treatment step.
  - Patients in all treatment steps were considered for eligibility.
- The study sample was limited to those who remained in remission until the end of any given treatment phase and then progressed into the 12-month naturalistic follow-up phase. Study sample patients were stratified into 2 cohorts:
  - **Early remitters** were defined as patients achieving remission ≤28 days following treatment initiation at step start.
  - **Late remitters** were defined as patients achieving remission >28 days following treatment initiation at step start.
- Relapse was defined as QIDS-SR_{16} score ≥11 during the 12-month follow-up phase, and ≥7 days after the date of remission, and identified in the early remitters and late remitters cohort.
- Two-sided Fisher's exact test was used to compare the proportions of patients who experienced relapse between cohorts (ie, late vs early remitters).
- Time to relapse was defined in days from treatment phase exit (naturalistic follow-up start) to time of first relapse or end of follow-up for censored patients.
- A Kaplan-Meier plot of the product-limit estimates for time to relapse by early vs late remitters is presented and survival curves compared using the log-rank test.
- Cox regression model was used to estimate the hazard ratio between early vs late remitters and subsequent time to relapse, adjusted for patient age, treatment step, and QIDS-SR_{16} score at step start.
  - Additional demographic factors (ie, education level, household size, and public assistance) were chosen using forward selection with P<0.05 inclusion criteria.

Results

Demographics and baseline characteristics

- Across all steps, a total of 1,130 patients with MDD achieved remission in the STAR*D trial, with 231 (20.4%) patients achieving early remission (≤28 days) and 899 (79.6%) achieving late remission (>28 days).
- At baseline, late remitters were more likely to be female (P=0.001), older (P=0.024), and more severely depressed (P<0.001) compared with early remitters (**Table 1 and 2**).
- Significant differences were also seen at baseline with marital status (P=0.004), student status (P=0.020), and the total number of persons living in the household (P=0.013) between early and late remitters (**Table 1 and 2**).
- The relative proportions of early and late remitters in each study step did not differ significantly (P=0.300, **Table 1**).

Table 1. Baseline patient characteristics (categorical) by early versus late remission status

Variable, n (%)	Early remission (N=231)		Late remission (N=899)		P value[a]
Female	124	(53.7%)	585	(65.1%)	**0.001**
Lives with spouse/partner	119	(66.9%)	421	(65.6%)	0.750
Current marital status					**0.004**
Never married	70	(30.3%)	240	(26.7%)	
Married/partner	122	(52.8%)	410	(45.7%)	
Separated/divorced/widowed	39	(16.9%)	248	(27.6%)	
Grade/Highest education					0.890
Graduate school	29	(12.6%)	125	(13.9%)	
College diploma or higher	59	(25.5%)	207	(23.1%)	
Associate / Technical degree	26	(11.3%)	113	(12.6%)	
HS/GED	100	(43.3%)	381	(42.4%)	
None	17	(7.4%)	72	(8.0%)	
Currently a student					**0.020**
No	184	(79.7%)	768	(85.5%)	
Yes	33	(14.3%)	74	(8.2%)	
Part time	14	(6.1%)	56	(6.2%)	
Current employment status					0.580
Unemployed not looking	34	(14.7%)	152	(17.1%)	
Unemployed looking	28	(12.1%)	111	(12.5%)	
Full time/ Self-employed for pay	116	(50.2%)	463	(52.0%)	
Part time employed for pay	32	(13.9%)	106	(11.9%)	
Retired not working	21	(9.1%)	59	(6.6%)	
Insurance					0.670
Medicaid	12	(5.2%)	51	(5.7%)	
Medicare	9	(3.9%)	28	(3.1%)	
Other/Unknown	65	(28.1%)	286	(31.8%)	
Private	145	(62.8%)	534	(59.4%)	
Treatment step of achieving remission					0.300
1	170	(73.6%)	669	(74.4%)	
2	56	(24.2%)	196	(21.8%)	
3	5	(2.2%)	22	(2.5%)	
4	0	(--)	12	(1.3%)	
Total number of persons in household					**0.013**
1	30	(13.0%)	211	(23.5%)	
2	85	(36.8%)	302	(33.7%)	
3	48	(20.8%)	147	(16.4%)	
4	39	(16.9%)	136	(15.2%)	
5+	29	(12.6%)	101	(11.3%)	

[a]Pearson's chi-square test

Table 2: Baseline patient characteristics (continuous) by early versus late remission status

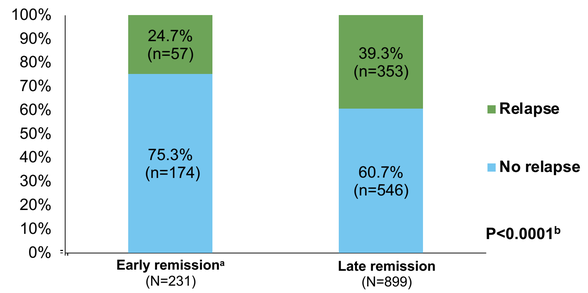
Variable, mean (SD)	Early remission (N=231)		Late remission (N=899)		P-value[a]
Age (years)	40.3	(13.9)	42.5	(12.8)	**0.024**
Total number of persons in household	2.8	(1.4)	2.6	(1.5)	0.070
Number of years in formal education	14.3	(3.2)	14.2	(3.2)	0.830
Monthly household income ($)	2910.0	(3,072.0)	2897.0	(3,382.0)	0.960
QIDS-SR TS at baseline	11.6	(3.8)	13.8	(4.1)	**<0.001**

Abbreviations: QIDS-SR16, Quick Inventory of Depressive Symptomatology; SD, standard deviation; TS, total score
[a]Two-sample 2-sided t-test

Unadjusted rates of relapse by early vs late remitters

- A significantly higher proportion of late remitters (39.3%) relapsed during the 12-month follow-up phase compared with early remitters (24.7%, P<0.0001**, Figure 1**).

Figure 1. Unadjusted rates of relapse by early versus late remission status

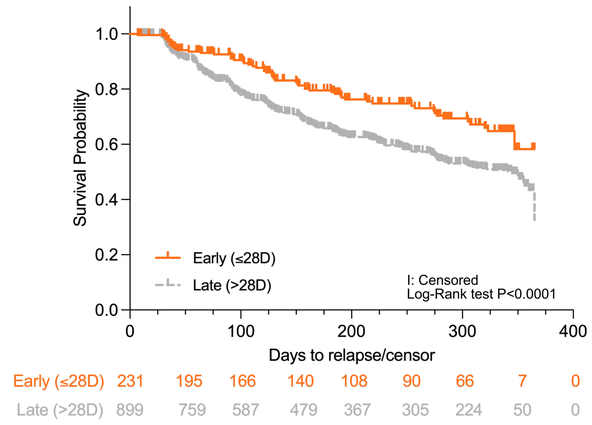


[a]Early remission in step based on first QIDS-SR16 ≤5 before or on Day 28 of treatment and sustained remission through step exit
[b]Fisher's Exact two-sided test for 2 level categorical variables

Mean product-limit estimates for time to relapse between early versus late remitters

- Accounting for censorship, the mean time to relapse was 282.5 days and 251.6 days for early remitters and late remitters, respectively.
- The probability of relapse was higher for late remitters than early remitters beginning at ~day 25 post-remission (P<0.0001, **Figure 2**).

Figure 2. Follow-up time to relapse after remission over all four treatment steps



Adjusted Cox model of time to relapse

- The adjusted relapse hazard among late remitters was nearly 1.5 times that of patients experiencing early remission (P=0.01, **Table 3**).
- Baseline QIDS-SR_{16} score (P<0.0001) and education level were also significant predictors of relapse hazard (P=0.0001); individuals who had no education had twice as likely relapse hazard, compared with those with a graduate school education (P=0.001, **Table 3**).
- Individuals who received public assistance had approximately 1.5 times the hazard of relapse compared to those who did not receive public assistance (**Table 3**).
- Smoothed scaled Schoenfeld residuals plots and tests showed no evidence of nonproportional hazard.

Table 3. Cox regression model for time to relapse of late vs early remitters[a,b]

	Hazard ratio	95% CI	P-value[c]
Late remission (>28 days)[d]	1.5	1.1, 2.0	**0.0097**
Age (years)	1.0	1.0, 1.0	0.374
Baseline QIDS-SR_{16} total score (at step start)	1.1	1.0, 1.1	**<0.0001**
Step (reference=step 1)			**<0.0001**
Step 2	1.9	1.4, 2.3	**<0.0001**
Step 3	1.7	0.9, 3.2	0.129
Step 4	2.4	1.1, 5.2	**0.023**
Education level (reference=graduate school)			**0.0001**
College diploma	1.0	0.7, 1.5	0.996
Associate/technical degree	1.1	0.7, 1.7	0.590
HS/GED	1.6	1.1, 2.2	**0.014**
None	2.1	1.4, 3.4	**0.001**
Total number of persons in household (reference=1 for self)			**0.015**
2	0.9	0.7, 1.1	0.315
3	1.0	0.7, 1.4	0.970
4	1.1	0.8, 1.5	0.579
5+	0.5	0.3, 0.8	**0.004**
Received public assistance (reference=0)	1.5	1.1, 2.1	**0.004**

Abbreviations: CI, confidence interval; GED, general education development; HS, high school; QIDS-SR16, Quick Inventory of Depressive Symptomatology Self-Report
[a]N=1130, N=1061 observations used.
[b]Variable selection: age, step, and step baseline QIDS-SR16 were forced into the model. Forward selection used for all other demographic characteristics with no other baseline outcome measures.
[c]Wald's chi-square test.
[d]The interaction term for Late remission* Step was not significant when added to this model (P=0.914).
[e]Public assistance includes federal/state programs for low-income persons

Limitations

- The study used a self-reported scale (QIDS-SR_{16}) to assess symptoms of remission and relapse over the previous 7 days, whereas MDD is typically diagnosed based on symptoms that persist over a minimum of 2 weeks. This may limit the ability to generalize the study findings to individuals with MDD who experience symptoms for longer durations.
- Additionally, since a placebo treatment was not incorporated into any stage of the study, we cannot ascertain whether the observed outcomes may have been influenced by factors other than the antidepressant treatments themselves.
- Lastly, it is important to note that regression analyses may only identify associations, and not necessarily causality.

Conclusions

- Patients in the STAR*D trial, who remitted earlier (≤28 days following step start), showed a significantly reduced risk of relapse and a longer period of remission compared to those remitting later.
- Other significant predictors of MDD relapse included higher baseline QIDS-SR_{16} total score, lower education level, and receiving public assistance.
- These findings highlight the importance of quickly inducing remission– both for the early relief of symptoms and the improvement of long-term outcomes.
- Optimal treatment sequencing strategies, but more critically, novel rapid-acting pharmacotherapies, remain areas of important unmet medical need.

Abbreviations

CI, confidence interval; D, day; GED, general education development; HS, high school; MDD, major depressive disorder; QIDS-SR16, Quick Inventory of Depressive Symptomatology Self-Report; SD, standard deviation; STAR*D, Sequenced Treatment Alternatives to Relieve Depression TS, total score

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