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

#CO200

Abhishek Chitnis, PhD[1]; Lasair O'Callaghan, MPH[2]; Ellison Suthoff, MBA[2]; Andy Czysz, MD[2]; Ramon Iovin, PhD[1]; Alice Kate Cummings Joyner, MS[3]; Warren Stevens, PhD[3]; Moshe Fridman, PhD[4]

[1]Biogen Inc., Cambridge, MA, USA [2]Sage Therapeutics, Inc., Cambridge, MA, USA [3]Medicus Economics, LLC, Boston, MA, USA [4]AMF Consulting, Los Angeles, CA, USA

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

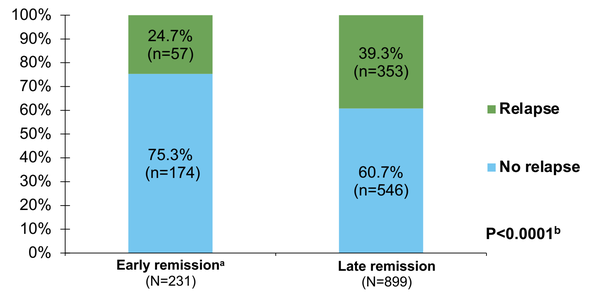
Variable, mean (SD)	Early remission (N=231)		Late remission (N=899)		P-value[a]
Age (years)	40.3	(13.9)	42.5	(12.8)	**0.024**
Total number of persons in household	2.8	(1.4)	2.6	(1.5)	0.070
Number of years in formal education	14.3	(3.2)	14.2	(3.2)	0.830
Monthly household income ($)	2910.0	(3,072.0)	2897.0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

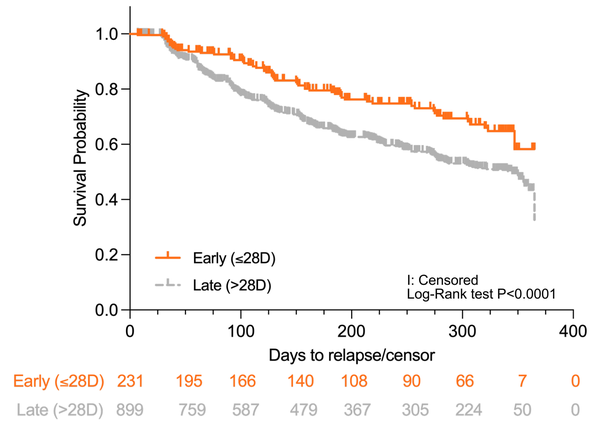


[a]Early remission in step based on first QIDS-SR16 ≤5 before or on Day 28 of treatment and sustained remission through step exit
[b]Fisher's Exact two-sided test for 2 level categorical variables

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

Acknowledgments

This study was sponsored by Sage Therapeutics, Inc. (Cambridge, MA, USA) and Biogen Inc. (Cambridge, MA, USA). Writing and editorial support for the preparation of this poster were provided by Boston Strategic Partners, Inc. (Boston, MA, USA); funding was provided by Sage Therapeutics, Inc. and Biogen Inc. Data used in the preparation of this abstract were obtained from the National Institute of Mental Health (NIMH) Data Archive (NDA). Dataset identifier(s): [NIMH Data Archive Digital Object Identifier (DOI) 10.15154/1528129].

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Disclosures: AC and RI are employees of Biogen Inc. and may hold stock. LOC, ES and AC are employees of Sage Therapeutics, Inc. and may hold stock and/or stock options. AKCJ and WS are employees of Medicus Economics, LLC, which was paid by Sage Therapeutics, Inc. and Biogen Inc. to conduct the research reported in this work. MF is the owner and an employee of AMF Consulting, which was funded by Sage Therapeutics, Inc. and Biogen Inc. to conduct the research reported in this work.

abhishek.chitnis@biogen.com