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Presenting characteristics of depressed outpatients as a function of recurrence: Preliminary findings from the STAR*D clinical trial

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Abstract

Objectives—Recurrent depression predicts risk for subsequent episodes, but it is unclear how it relates to demographic features, course of illness, and clinical presentation.

Methods—We report on the baseline data for the first 1500 patients enrolled in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (www.star-d.org). Patients were required to have a DSM-IV diagnosis of nonpsychotic major depression and to score ≥ 14 on the 17-item Hamilton rating scale for depression. Status with respect to recurrent depression and other aspects of illness course and demographic features were ascertained at intake, along with measures of depression and concurrent general medical illness.

Results—Patients with recurrent depression were older, had an earlier age of onset, and were more likely to have a positive family history of depression than first episode patients. However, recurrent patients were less likely to be chronic and reported shorter current episodes than first episode patients, something that was largely confined to females. Recurrent patients were more likely than first episode patients to report non-essential aspects of mood, cognition, and somatic symptoms, although largely as a consequence of greater overall depressive symptom severity.

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Conclusions—As compared to single episode depressions, recurrent depression was associated with greater symptom severity and illness characteristics suggestive of greater underlying risk, but not other demographic characteristics than age. Risk for recurrence appeared to be distinct from chronic depression. A subset of chronic first episode patients may lack the capacity to remit and may therefore be distinct from those with recurrent episodes.

Keywords

Depression; Recurrent; Chronic; Risk

1. Introduction

Major depression is one of the most prevalent of the psychiatric disorders with a lifetime prevalence of 16.2% and high rates of comorbidity and impairment (Kessler et al., 2003). Up to a third of all patients will have episodes that last longer than two years, and the rate of recurrence is over 75%, making recurrence the rule rather than the exception (Keller, 2001). Although recurrent depression is known to predict risk for subsequent episodes, little is known about its correlates with other aspects of depression (Kupfer, 1991).

This report examines the demographic features, history of illness, and clinical presentation of patients with and without recurrent depression from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Fava et al., 2003; Rush et al., 2004). STAR*D participants are self-declared outpatients (i.e., no symptomatic volunteers or media-recruited subjects) presenting at 18 primary care and 23 specialty care clinical sites. STAR*D eligibility criteria are broadly inclusive, while exclusion criteria are limited (see below). Thus, findings from this study should generalize to most patients seeking outpatient treatment for nonpsychotic major depressive disorder (Fava et al., 2003).

While STAR*D is still ongoing, the available data on the first 1500 enrollees provide an opportunity to compare the baseline clinical and demographic features of participants with and without a history of recurrence. We wished to determine:

- Whether recurrent patients differ from single episode patients on socio-demographic features, course of depressive illness, and clinical presentation of depression (e.g., severity, symptom profiles, suicidal risk, and concurrent general medical conditions).
- Whether the current definition of recurrence (two or more episodes) is reasonable, or whether it is better to define recurrence by a larger number of episodes, as is sometimes done in clinical trials (e.g., Frank et al., 1990).

2. Methods

2.1. Study description and organization

The rationale and design of STAR*D are detailed elsewhere (Fava et al., 2003; Lavori et al., 2001; Rush et al., 2004). In brief, STAR*D will define prospectively which of several treatments are most effective for outpatients with nonpsychotic major depressive disorder (MDD) with an unsatisfactory clinical outcome to an initial and, if necessary, subsequent

treatment(s). Eligible and consenting STAR*D enrollees are treated initially with a selective serotonin reuptake inhibitor. Those not achieving symptom remissions may enter one or more subsequent randomized trials that involve different sequences or combinations of medications or cognitive therapy through a total of four additional possible levels. Patients with an adequate clinical response to treatment at any level enter a 12-month naturalistic follow-up phase.

The STAR*D infrastructure includes the National Coordinating Center in Dallas (NCC), the Data Coordinating Center in Pittsburgh (DCC) and 14 Regional Centers (RCs), each of which oversees 2–4 clinical sites providing primary or specialty care to either public or private sectors. Nearly half of the clinical sites (18 of 41) are primary care settings. Clinical sites were identified based on multiple factors including the availability of depressed outpatients, clinicians, administrative support, and minority populations.

Clinical Research Coordinators (CRCs) located at the clinical sites are trained and certified in implementing the treatment protocol and in data collection methods (i.e., screening procedures, inclusion and exclusion criteria, data items to be collected, and procedures to complete data forms). CRCs work closely with participants and clinicians, administer some of the clinician-rated instruments, ensure that all self-rated instruments are completed, and function as study coordinators, providing a liaison between the clinical sites and the Regional Centers. Research outcome data are collected via telephone interviews with trained Research Outcomes Assessors (ROAs), masked to treatment and to treatment settings, and a telephone-based interactive voice response (IVR) system (Kobak et al., 1999).

The study was carried out in accordance with the latest version of the Declaration of Helsinki and the appropriate ethical committee at each participating institution reviewed the study design. Informed consent was obtained after the nature of the procedures had been fully explained to each potential participant.

2.2. Study population

Self-declared outpatients presenting at participating clinics and identified by their clinician as having a depression requiring treatment were approached to consider participating in STAR*D. All potential benefits and risks (including possible adverse events) associated with the trial were explained to potential participants prior to obtaining written informed consent. All subjects were between the ages of 18 and 75 (inclusive) and met DSM-IV criteria for single or recurrent, nonpsychotic major depressive disorder (American Psychiatric Association, 1994). Participants also were required to score ≥ 14 (moderate severity) on the 17-item version of the Hamilton depressive rating scale (HAM-D₁₇) as rated by the CRC to ensure sufficient symptom severity that symptom change could be measured during the trial (Hamilton, 1961). This level of severity indicates a clear need for treatment and reflects a level of depression for which medication is superior to placebo (Fava et al., 2003; Paykel et al., 1988a,b).

Patients were excluded who met criteria for bipolar disorder or exhibited psychotic symptoms (lifetime), had a current primary diagnosis of obsessive compulsive or eating disorders, suicidal risk or substance abuse/dependence that required inpatient care, or a

seizure disorder or other general medical condition contraindicating medications used in the first two levels of the study. All other psychiatric and medical comorbidities were allowed. Women who were pregnant or breastfeeding were also excluded, as were patients who had not satisfactorily responded to an adequate treatment trial of a study medication during their current major depressive episode. Exclusion criteria were kept to a minimum to ensure that the findings generalized to clinical practice in applied settings.

2.3. Assessments

CRCs collected standard demographic information and self-reported psychiatric history at baseline and rated the severity of depressive symptoms with the HAM-D₁₇. They also evaluated current general medical conditions on the Cumulative Illness Rating Scale (CIRS), a 14-item interview that gauges the severity/morbidity of general medical conditions relevant to different organ systems (Linn et al., 1968). The ROA used a telephone interview at baseline to collect a second HAM-D₁₇ (Simon et al., 1993) and the 30-item Inventory of Depressive Symptomatology (IDS-C₃₀) (Rush et al., 1996), a well-studied tool that uses unconfounded items to measure both core criterion diagnostic symptoms and associated symptoms of depression.

The number of prior episodes was assessed at intake by the CRC as part of the illness history, along with length of current episode and age at first onset. These estimates were based on patient self-report and supporting information in patient charts. Recurrence was defined as two or more discrete episodes of depression (including the present episode). Depressions were considered chronic if the current episode had lasted for at least two years regardless of recurrence (APA, 1994).

2.4. Data analysis

Because we were interested not only in the correlates of recurrence but also the utility of the way it is currently defined, we conducted analyses treating recurrence both categorically (first episode versus two or more episodes) and ordinally (specifying number of episodes). If there are better ways of defining recurrence, this might be suggested by the pattern of correlates with alternate numbers of episodes. Moreover, if number of episodes (beyond two) is related to underlying risk, then retaining information regarding episode frequency should increase correlations with related indices of risk. Potential correlates included a number of demographic and course of illness variables, as well as responses to the measures of comorbid medical conditions and depressive symptoms. A series of univariate analyses of variance were applied to the continuous measures, treating recurrence (or total number of episodes) as the classifying variable. Nonparametric analyses were used for categorical measures. Alpha was set at $p=.05$ level in all instances; the experiment-wise error rate was not controlled in what were considered largely exploratory analyses. Means and standard deviations were reported for the continuous measures, and percentages were reported for categorical data and for the probability of endorsement on the IDS-C₃₀ items.

Given the potential confounding effects of age and time since first onset of MDD (people who are older or who have been depressed longer have more time to have subsequent episodes), we performed additional analyses controlling for each (the latter only in

combination with age). Controlling for age is sensible, since effects related to the mere passage of time provide little useful information about underlying causal processes. It is more problematic conceptually to control for time since first onset of MDD, since the latter is determined in part by age of onset, which may itself be related to the very causal process that put patients at risk for recurrence. Controlling for time since first onset of MDD further adjusts for the simple passage of time (since patients with an earlier age of onset have more time for subsequent episodes than patients with a later age of onset), but also risks removing causal variance related to underlying risk (Meehl, 1971). We control both for age alone and age plus time since first onset of MDD in separate sets of analyses, recognizing that neither is ideal (the former controls for too little and the latter controls for too much). We also identified the presence or absence of chronic depression and repeated all of the above analyses within each set of patients. Finally, given our interest in specific symptoms, we conducted additional analyses that controlled for severity (in conjunction with age) to see if different symptom profiles emerged over and above the influence of overall severity and age.

The following text uses the term recurrent (or recurrence) to refer to patients who met DSM-IV criteria for recurrent depression (two or more episodes) and differentiates these findings from those obtained when we classified patients based on number of episodes. In those latter instances, we also describe the pattern observed to see if it increased in a consistent fashion as the number of episodes increased (as it should if recurrence is a unified construct).

3. Results

3.1. General

This report provides information on the first 1500 participants enrolled in the project. These patients represented 74% of a larger pool of 2026 individuals screened for the study. Of the 26% screened but not enrolled, 14% were found to be ineligible and 12% were eligible but declined consent. Just over a third of the participants enrolled came from primary care settings ($n = 512$), while just under two thirds of the participants presented at specialty care settings ($n = 988$). The sample was predominantly female (60%), white (75%), and non-Hispanic (88%). Most were currently employed (59%), and the modal patient was currently married (46%).

3.2. Distribution of recurrence rates

Information regarding number of episodes was available on most patients ($N = 1426$). Specialty care sites were twice as likely to have missing data than primary care sites (6.0% v. 3.1%; $p = .017$). For those patients on whom we had information regarding the number of prior episodes, over a quarter (26%) reported being in their first major depression episode, whereas the majority (74%) met DSM-IV criteria for recurrence. Fig. 1 shows the distribution of reported episodes, aggregating across less frequent categories. The median patient reported being in his or her third episode, with decreasing numbers of patients reporting four through nine episodes (these latter patients are aggregated in the figure). A small minority of patients (18%) reported 10 or more episodes, up to a maximum of “too many to recall”. It is likely that these higher estimates were less precise than those in the single digits, since they typically clustered around multiples of 10. In other respects, before

aggregation, the number of patients in each category typically decreased with increasing numbers of episodes. This suggests that number of episodes is monotonically distributed within the clinical population, although truncated and skewed right. Deviations from this smooth distribution beyond the ninth episode were likely a consequence of imprecision in estimation among patients who experienced a large number of episodes.

3.3. Demographic factors and recurrence

Table 1 presents the baseline demographic characteristics of these 1426 patients. It first compares patients in their first episode to those who are recurrent (regardless of number of episodes) and then compares those in their first episode to those in their 2nd, 3rd, 4th through 9th, and 10th or more episode. Means and standard deviations are provided for the continuous variables, and percentages are provided for the categorical variables. Tests of significance are provided for the first versus any recurrent episode and then for specific numbers of episodes (including the first episode) to examine the effects of increasing numbers of episodes. Significance levels are also provided controlling for age (in parentheses), age plus time since first onset of MDD {in fluted brackets}, and age plus overall severity [in square brackets]. These comparisons provide our best estimate of the descriptive differences between recurrent and non-recurrent patients, as recurrence is currently defined.

Table 1 shows that recurrent patients were older than first episode patients and that number of episodes typically increased with age. There were few differences based on other demographic characteristics. Recurrent patients were better educated than first episode patients (even after controlling for age), although differences were modest in magnitude and largely specific to a single subset of patients (those reporting four to nine episodes). Hispanic patients reported experiencing fewer episodes than did non-Hispanic patients, although differences were significant only when specific numbers of episodes were taken into account and were most apparent among patients with at least four episodes. With respect to employment and marital status, both retirement and divorce were associated with recurrence or greater numbers of episodes, but not after controlling for age. Gender, race, household income, and treatment setting were largely unrelated to recurrence or number of episodes.

3.4. Illness-related characteristics and recurrence

Recurrent patients were not only older than first episode patients, but also had an earlier age of onset, as shown in Table 2. Recurrent patients, therefore, had a longer time since first onset of MDD, even when controlling for age. Differences in age were most apparent for patients reporting four or more episodes (see Table 1), whereas age of first onset was visibly lower for patients reporting two or more episodes (see Table 2). As a consequence, time since first onset of MDD appeared to be clearly related to frequency of recurrence.

Although both age and time since first onset of MDD likely are related to number of episodes due to the passage of time, it is likely that time since first onset of MDD also is related to the causal processes that contribute to risk for depression since it is determined in part by age of first onset. Given that there is no way to remove all the spurious variance

related to the passage of time without also removing some of the causal variance related to underlying risk, we tried to estimate the relations between the constructs as best we could by conducting parallel sets of analyses that were either overly liberal (controlling for age alone) or overly conservative (controlling for age and time since first onset of MDD). For example, as also shown in Table 2, recurrent patients were more likely to have a family history of depression than were first-episode patients even when we controlled for age, but not when also we controlled for number of years since first onset of MDD. Since number of years since first onset of (which is itself a function of age minus age of onset) can have no direct effect on whether other family members ever become depressed and family history can have no direct effect on number of years since first onset, family history and age of onset must share some common causal process. Family history is unlikely to be influenced by how long a patient has been depressed, but it is likely that the same processes that put some families at increased risk may also contribute to earlier age of onset and subsequent risk for recurrence.

Table 2 also shows that recurrent patients reported having shorter current episodes and were less likely to meet the criteria for chronic depression (18.9%) than were first episode patients (43.6%). This is striking, since length of episode was the only feature that was negatively related to recurrence. Recurrent patients did not always differ from non-recurrent patients, but when they did, recurrent patients typically evidenced more as opposed to less pathology than did first episode patients. This propensity for recurrent patients to have briefer episodes probably reflects the fact that patients must first recover from their initial episodes in order to have a subsequent episode.

Moreover, it suggests that first episode patients likely represent a diverse group with respect to risk for recurrence. Some patients will recover from their initial episode and never have another; whereas others will recover and go on to have a history of recurrence. It is the comparison between these two sets of patients, both of whom have the capacity to recover from a given episode that most people have in mind when they explore the correlates of recurrence. However, there is also a third set of patients who may never recover from the initial episode. These latter patients may have a lower capacity for recovery than do patients who get better. This lower capacity for recovery is as likely to be associated with elevations in other aspects of psychopathology as the propensity for recurrence. As a consequence, mixing chronic and non-chronic first episode patients could obscure differences between first episode patients with a capacity for recovery who differ in risk for subsequent recurrence.

We, therefore, evaluated the length of the current episode in relation to the number of episodes in chronic and non-chronic patients. Fig. 2 shows that chronic patients had longer episodes than non-chronic patients at every frequency of recurrence, but that this was especially true for first episode females and second episode males. This is consistent with the notion that there exists a subset of patients (mostly females) who may never recover from their first episode or go a very long time without recovering and a smaller subset of patients (mostly male) who report extremely long second episodes (for which we have no good explanation). As a consequence, we stratified our sample by length of current episode and gender and ran separate sets of analyses within chronic and non-chronic patients stratified by gender. There were few clear differences between chronic and non-chronic

patients (even within the separate genders), suggesting that the inclusion of chronic patients among the first episode patients did not obscure differences as a function of recurrence.

3.5. Symptomatic presentations and recurrence

Table 3 shows that patients with recurrent depression reported higher total scores and endorsed a greater number of different categories of concurrent general medical conditions on the CIRS than did first episode patients, even after controlling for age. These differences were largely attributable to patients with 10 or more episodes, who reported the greatest number of comorbid medical illnesses. Recurrent patients also reported greater levels of depressive symptom severity on both the HRSD₁₇ and the IDS-C₃₀, with scores typically increasing somewhat as a function of number of episodes. Differences were most striking on the IDS-C₃₀ and showed their biggest increment between the first and second episode.

To examine the symptomatic presentations of MDD in single episode and recurrent patients, we compared the individual items on the IDS-C₃₀ for the two groups. We calculated the percentage of patients in each group for whom the symptom was endorsed (i.e., rated 1) (Table 4), and the mean scores for each item (data not shown). Results were virtually identical using these two calculations. Table 4 reports overall rates of endorsement of symptoms for recurrent patients in aggregate and for patients with each frequency of recurrent episodes. As in the earlier tables, significance levels are adjusted separately for age alone and for age plus time since first onset of MDD and age plus severity on the larger instrument.

On the whole, these patterns suggest that recurrent patients experienced more symptoms than first episode patients, especially with respect to non-essential aspects of mood, cognition, and somatic symptoms, although differences were rarely large in magnitude. The largest discrepancy reported between single episode and recurrent patients was 9.5% on sympathetic arousal, and the largest discrepancies reported overall were just greater than 12% between first episode patients and those with 10 or more episodes on anxious mood, panic/phobia, and agitation. When differences were apparent, recurrent patients typically reported more symptoms than first episode patients, and the number of symptoms reported typically increased with number of episodes (if they increased at all). These differences often disappeared or diminished markedly when overall severity was controlled.

3.6. How adequate is the current definition of recurrence?

Finally, we wanted to examine the adequacy of the current definition of recurrence. If first episode patients are distinct from those with two or more episodes, then to define recurrence in this categorical way is useful. If first episode patients are not distinct from those with two or more episodes but symptoms and other indices increase with number of episodes, then recurrence is more continuous in nature and the current definition is no better or worse than any other. But if a natural discontinuity occurs at some other point beyond the first episode, then recurrence may be better defined in a categorical way that is not well represented by the current consensus definition.

To explore this question, we ranked each of the episode frequencies reported in the tables from lowest (first) to highest (fifth) on each of the demographic, illness-related, and

symptom variables previously described. Determining the direction of greatest pathology for the illness-related and symptom variables was relatively straightforward; for the demographic variables the direction was inferred from the general ordering of the episode frequencies. We then calculated the proportion of times that groups of patients with a given episode frequency occupied each of the ranks.

As shown in Fig. 3, there was a general and orderly progression. First episode patients reported the lowest or least pathological scores on the indices or measures over 60% of the time, far more often than any other group of patients. Patients with two episodes were most likely to rank second, patients with three episodes were most likely to rank third, and patients with four through nine episodes were most likely to rank fourth, all with probabilities of around 40%. Patients with 10 or more episodes, the most recurrent patients, had the highest scores on the respective indices nearly 50% of the time, considerably more than any other group of patients.

Moreover, these patterns were relatively orderly within groups of patients defined by number of episodes; first episode patients were most likely to report the lowest scores among all patients, but when they did not, they were next most likely to rank second or third and least likely to rank fourth or fifth. On this metric, second episode patients looked more like other recurrent patients than they did like first episode patients; that is, if they did not rank second, they were more likely to rank third or fourth or fifth (in descending order) than they were to rank first. Similar patterns held for patients with three or four-to-nine episodes.

Thus, patients with two or more episodes were more similar to one another than they were to first episode patients. This increases our confidence in the current definition of recurrence. The only deviation from this pattern occurred among patients who reported 10 or more episodes, who were disproportionately likely to be ranked lowest on an index or symptom if they were not ranked highest (as they typically were). This pattern was largely a consequence of the disproportionate number of unemployed, low income black males found in primary care settings (these variables accounted for the five instances in which patients with 10 or more reported episodes had the lowest rankings). It may be that such patients tend to over-report other symptoms (or even the number of episodes), since they stood out from other patients even more than would be expected on the basis of having the greatest number of episodes (when they were ranked highest on a variable they were often disproportionate in their elevation). Nonetheless, the overall pattern is one of an orderly progression within multiple episode patients with the greatest evidence of discontinuity occurring between single episode and multiple episode patients.

4. Conclusions

There were few demographic differences between recurrent and single episode patients that could not be attributed to age (though Hispanic patients did report fewer episodes), suggesting that risk for recurrence is distributed uniformly across different kinds of people and cannot be predicted by simple demographic characteristics. That number of episodes (and hence likelihood of recurrence) increased as a function of age was not surprising, since the longer someone lives the more time is available for subsequent episodes. More

interesting conceptually was the finding that recurrence was also related to age of first onset, even after controlling for age, since people with a greater underlying risk for multiple episodes might be expected to have an earlier age of onset. Indeed, patients with a family history of depression also were more likely to be recurrent and to have an earlier age of onset. If recurrence were simply a function of time at risk, it is not clear why it should be related to family history. In aggregate, these findings suggest that recurrence is associated with some type of underlying risk that is distributed within families and increases the likelihood of early onset (Costello et al., 1992).

The one aspect of history of illness that is not associated with greater risk for recurrence is the propensity for chronic depression. In fact, patients were less likely to be recurrent if they met criteria for chronic depression than if they did not. It is probably not that being chronic affords “protection” from recurrence, but rather that a person must first recover from one episode in order to go on to have another. It is possible that the processes that confer risk for subsequent recurrence (onset) may be different from those that govern the capacity for remission (offset) and thereby determine episode length. Patients with chronic depression were disproportionately more likely to be found among the first episode patients (43.6%) than among those with a recurrent course of illness (18.9%). These chronic patients were no more likely to have family histories of depression than patients who did not meet criteria for chronic depression. This suggests that a subset of first episode patients may exist who do not remit, and who may be distinct from other first episode patients who do remit (including those who will go on to have multiple episodes). The recent development of novel interventions for chronic depression contributes to the possibility that such patients may constitute a distinct subtype of depression (McCullough, 2000). It will be interesting to see if these findings can be replicated in the remainder of the STAR*D sample and whether chronicity and recurrence each predict different aspects treatment outcome (with chronic patients less likely to respond to acute treatment and recurrent patients more likely to relapse during continuation). Curiously, there were different patterns across the genders, with women more likely to experience long first episodes and men more likely to do so in the second; something that needs to be further explored.

Descriptively, recurrent patients reported higher levels of depressive symptoms and a greater number and higher total scores on comorbid medical conditions than did first episode patients. Differences in specific symptoms were most apparent for non-essential aspects of mood like anxiety, as well as somatic and cognitive symptoms. In almost all instances, recurrent patients reported more of these symptoms than did first episode patients, and there was little evidence that the overrepresentation of chronic patients among the latter obscured differences as a function of recurrence. Few of these differences remained after controlling for severity, and it is likely that they reflected overall elevations associated with recurrence than any specific symptom profile.

Two caveats deserve mention. First, the ascertainment of number of episodes could have been done with greater sophistication. In most instances, patients were simply asked to report how many prior episodes they had experienced (as well as the length of the current episode), rather than tracing a more precise picture of episode onset and offset as is sometimes done in longitudinal research. These data were collected as part of a larger intake

battery in the context of an effectiveness study in applied clinical settings and it is likely that the precision of our estimates is lower than is sometimes the case in other research.

Second, given that we did not map out the duration of prior episodes or the degree of inter-episode recovery or underlying dysthymia, we do not have a good estimate of how much time each patient spent in episode. The best we could do was to estimate how long it had been since patients first became depressed (time since first onset of MDD) by means of subtracting the reported age of onset from the patient's current age. If there is something about the amount of time spent symptomatic that increases subsequent risk for recurrence, then it would have been better to know how much time a patient had spent in episode, rather than how long it had been since they first became depressed. Few of the findings disappeared when we controlled for age, although many became non-significant when we controlled for time since first onset of MDD. In the absence of any estimate of the time actually spent depressed, we risked removing variance related to the causes of recurrence when we tried to control for time spent symptomatic with a variable that was based (in part) on age at first episode.

Nonetheless, neither limitation should have biased the observations, just reduced their precision and made it treacherous to speculate about the direction of causal influence. Our major findings are that recurrence is related to familial factors and history of illness characteristics suggestive of underlying biological risk (but not to demographic factors other than age) and that risk for recurrence may be distinct from risk for chronic depression. The current convention of defining recurrence in terms of two or more episodes of major depression is supported by these findings. Given the exploratory nature of the analyses and the number of variables tested, these findings require replication. This is something that we plan to do (along with testing hypothesis regarding differential response and relapse) when data become available on the remainder of the sample in the larger project and their response to treatment.

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Fig. 1.
Number of Episodes (Recurrence).

Fig. 2.
Length of Current Episode as a Function of Recurrence and Chronicity by Gender.

Fig. 3.
Proportion of Indices at Each Rank as a Function of Number of Episodes.

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Baseline characteristics	Total (<i>N</i> = 1426)	1st Episode (<i>N</i> = 365)	Recurrent (<i>N</i> = 1061)	<i>P</i> -value ^a	
		Mean (SD)	Mean (SD)		
Demographic (continuous):	<i>N</i>				
				2nd Episode (<i>N</i> = 259)	Mean (SD)
				3rd Episode (<i>N</i> = 218)	Mean (SD)
				4–9 Episodes (<i>N</i> = 325)	Mean (SD)
				10 + Episodes (<i>N</i> = 259)	Mean (SD)
Specialty	930	63.3	65.9	66.0	66.5
				69.8	60.2

^aAdjusted for age (parentheses), age and time since first onset of MDD (fluted brackets), and age and severity [squared brackets].

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Table 2

History of illness as a function of recurrence

Baseline characteristics	Total (N = 1426)	1st Episode (N = 365)	Recurrent (N = 1061)	P-value ^a					
					2nd Episode (N = 259)	3rd Episode (N = 218)	4–9 Episodes (N = 325)	10 + Episodes (N = 259)	P-value ^a
History illness (continuous):	N	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age 1st MDE (years)	1424	33.8 (15.0)	22.4 (12.3)	<.0001	27.8 (13.5)	22.5 (10.9)	20.8 (11.9)	19.2 (11.1)	<.0001
Time since first onset of MDD (years)	1422	5.3 (8.1)	18.7 (12.9)	<.0001	12.3 (10.6)	17.0 (12.3)	20.8 (13.1)	24.1 (12.2)	<.0001
Current MDE (months)	1418	52.9 (95.2)	17.1 (38.2)	<.0001	23.2 (60.2)	18.5 (31.1)	14.2 (28.1)	13.6 (21.9)	<.0001
History illness (categorical):	N	%	%		%	%	%	%	
<i>Chronic MDE</i>									
Yes	358	43.6	18.9	<.0001	21.6	21.2	16.4	17.6	<.0001
No	1060	56.4	81.1		78.4	78.8	83.6	82.4	
<i>Family Hist Dep</i>									
Yes	783	46.3	58.2	<.0001	55.3	56.0	62.2	57.9	0.0002
No	637	53.7	41.8		44.7	44.0	37.8	42.1	

^a Adjusted for age (parentheses), age and time since first onset of MDD {fluted brackets} , and age and severity [squared brackets].

Table 3

Clinical presentation as a function of recurrence

Baseline characteristics	Total (N = 1426)	1st Episode (N = 365)		Recurrent (N = 1061)		P-value ^a	2nd Episode (N = 259)		3rd Episode (N = 218)		4-9 Episodes (N = 325)		10 + Episodes (N = 259)		P-value ^a
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)			
CIRS medical comorbidities	1426	2.6 (2.1)	3.2 (2.2)	3.2 (2.2)	[0.0067]	{0.0579}	(0.0010)	{0.0067}	3.1 (2.3)	2.9 (2.0)	3.6 (2.3)	{0.0589}	[0.0146]		
CIRS: categories endorsed															
CIRS: total score	1426	3.8 (3.6)	4.5 (3.6)	4.5 (3.6)	[0.1036]	{0.2158}	(0.0434)	{0.1036}	4.3 (3.5)	3.9 (3.2)	5.4 (3.9)	{0.0165}	[0.0239]		
CIRS: severity index	1426	1.2 (0.7)	1.2 (0.6)	1.2 (0.6)	[0.8035]	{0.8971}	(0.7241)	{0.8035}	1.1 (0.6)	1.2 (0.6)	1.4 (0.6)	{0.0495}	[0.4820]		
Symptom severity															
HRSD ₁₇	1372	19.6 (7.1)	20.7 (6.5)	20.7 (6.5)	[0.6364]	{0.2309}	(0.0040)	{0.6364}	20.9 (6.7)	20.5 (6.4)	21.2 (6.2)	{0.0974}	[0.6219]		
IDS-C ₃₀	1375	34.0 (12.5)	36.4 (11.3)	36.4 (11.3)	[0.0006]	{0.1935}	(0.0006)	{0.0006}	36.7 (12.4)	36.2 (10.9)	37.1 (10.5)	{0.0658}	[0.0006]		

^a Adjusted for age (parentheses), age and time since first onset of MDD {fluted brackets}, and age and severity [squared brackets].

Table 4

Specific symptoms as a function of recurrence

Baseline characteristics	Total (N = 1426)		1st Episode (N = 365)		Recurrent (N = 1061)		P-value ^d		2nd Episode (N = 259)		3rd Episode (N = 218)		4-9 Episodes (N = 325)		10+ Episodes (N = 259)		P-value ^d	
	%	N	%	N	%	N		%	N	%	N	%	N	%	N	%		N
Specific IDS-C₃₀ symptoms:																		
<i>Essential features:</i>																		
Depressed mood	96.8	1384	95.4	351	97.2	1033	0.1125	(0.0764)	{0.1473}	{0.5197}	98.0	252	96.7	210	97.2	317	96.9	254
<i>Anhedonia</i>																		
Involvement	87.3		85.5		87.9		0.2361	(0.1947)	{0.4561}	{0.8424}	83.4		87.6		91.2		88.6	
Pleasure	69.1		69.5		69.0		0.8448	(0.9234)	{0.4419}	{0.0748}	70.0		69.0		69.4		67.3	
<i>Core features: Mood-related</i>																		
Anxious mood	78.7		72.9		80.7		0.0024	(0.0029)	{0.1365}	{0.0503}	78.7		81.0		78.2		85.4	
Irritable mood	80.6		76.1		82.2		0.0125	(0.0048)	{0.4079}	{0.0611}	76.7		82.9		84.5		84.3	
Panic/Phobia	37.5		34.2		38.6		0.1382	(0.1399)	{0.8846}	{0.9118}	34.4		39.0		35.4		46.5	
Mood reactivity	72.0		69.2		72.9		0.1871	(0.1317)	{0.6849}	{0.9222}	70.4		73.3		74.1		73.6	
Mood variation	25.3		20.8		26.8		0.0255	(0.0190)	{0.0215}	{0.0864}	27.7		26.2		28.4		24.5	
Quality of mood	73.9		68.7		75.7		0.0096	(0.0127)	{0.0486}	{0.0627}	73.5		73.8		80.1		73.9	
<i>Appetite/weight</i>																		
Appetite decrease	47.6		47.3		47.7		0.9006	(0.7602)	{0.2985}	{0.5785}	53.8		49.0		44.8		44.1	
Appetite increase	22.4		20.8		22.9		0.4098	(0.3960)	{0.5618}	{0.6055}	17.0		20.5		24.6		28.7	
Weight decrease	34.0		34.3		33.8		0.8813	(0.9335)	{0.7037}	{0.4362}	33.6		38.6		34.7		29.1	
Weight increase	21.9		20.6		22.3		0.4892	(0.4389)	{0.9318}	{0.8908}	19.8		18.6		21.5		29.1	
<i>Sleep disturbance</i>																		
Onset insomnia	70.0		67.2		71.0		0.1889	(0.1527)	{0.5195}	{0.7481}	73.8		71.4		65.0		75.2	
Middle insomnia	83.3		77.4		85.3		0.0007	(0.0031)	{0.1222}	{0.0428}	85.0		84.8		83.6		88.2	
Early insomnia	55.7		52.7		56.7		0.1964	(0.3785)	{0.8618}	{0.6482}	57.7		55.7		52.4		61.8	
Hypersomnia	25.3		25.6		25.2		0.8816	(0.8054)	{0.6881}	{0.7867}	22.5		21.0		30.0		25.6	
<i>Sexual interest</i>																		
Sexual Interest	63.5		59.3		64.9		0.0585	(0.0547)	{0.0608}	{0.4757}	66.0		61.0		65.9		65.7	
<i>Somatic symptoms</i>																		

Baseline characteristics	Total (N = 1426)		1st Episode (N = 365)		Recurrent (N = 1061)		P-value ^a		2nd Episode (N = 259)		3rd Episode (N = 218)		4-9 Episodes (N = 325)		10+ Episodes (N = 259)		P-value ^d					
	%		%		%		%		%		%		%		%		%					
Specific IDS-C ₃₀ symptoms:																						
Somatic complaints	75.2		73.5		75.7		0.4055	(0.4275)	{0.8968}	[0.8367]	75.1		72.9		76.0		78.3		0.1901	(0.2145)	{0.6117}	[0.8053]
Sympathetic arousal	66.9		59.8		69.3		0.0011	(0.0025)	{0.1447}	[0.0658]	68.8		67.1		68.1		73.2		0.0012	(0.0067)	{0.1883}	[0.1400]
Gastrointestinal	45.8		40.9		47.5		0.0306	(0.0647)	{0.2912}	[0.3342]	43.1		51.4		49.2		46.6		0.0408	(0.1145)	{0.3970}	[0.5491]
Leadens paralysis	45.1		39.0		47.1		0.0088	(0.0139)	{0.6483}	[0.2451]	47.4		43.3		46.4		50.8		0.0088	(0.0230)	{0.5408}	[0.3404]
Fatigue/Energy	91.1		88.0		92.2		0.0195	(0.0116)	{0.1383}	[0.1460]	92.9		91.4		93.4		90.6		0.1327	(0.0759)	{0.3085}	[0.4033]
Psychomotor																						
Slowing	63.7		60.1		64.9		0.1079	(0.1690)	{0.2968}	[0.7756]	63.2		66.2		65.6		64.6		0.1591	(0.2893)	{0.1774}	[0.5401]
Agitation	61.2		58.1		62.2		0.1771	(0.1789)	{0.7633}	[0.7444]	59.7		62.4		57.4		70.5		0.0216	(0.0183)	{0.1519}	[0.2052]
Cognitive																						
Worthless/guilt	81.5		76.4		83.3		0.0042	(0.0016)	{0.4063}	[0.0397]	77.1		82.8		89.3		82.3		0.0003	(<.0001)	{0.0617}	[0.0028]
Outlook future	79.6		74.9		81.1		0.0129	(0.0063)	{0.2859}	[0.1144]	82.6		79.0		81.4		81.1		0.0660	(0.0320)	{0.8207}	[0.3213]
Concentration	89.6		88.6		89.9		0.4782	(0.4094)	{0.5972}	[0.7117]	88.9		90.5		88.6		92.1		0.2692	(0.2195)	{0.1025}	[0.9082]
Suicidal Ideation	48.7		44.4		50.1		0.0674	(0.0600)	{0.9482}	[0.5612]	46.2		50.5		53.3		49.6		0.0460	(0.0443)	{0.6549}	[0.4496]
Interpersonal symptoms																						
Rejection sensitivity	58.8		53.3		60.7		0.0143	(0.0067)	{0.1703}	[0.1011]	55.3		66.2		62.1		59.8		0.0193	(0.0062)	{0.0992}	[0.1026]

Adjusted for age (parentheses), age and time since first onset of MDD {fluted brackets}, and age and severity [squared brackets].