Abrupt Symptom Improvements in Antidepressant Clinical Trials:

Transient Placebo Effects or Therapeutic Reality?

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ABSTRACT

Background: According to prevailing models and classical reports, abrupt responses to antidepressant medication are not true drug responses but rather transient placebo effects. By contrast, recent reports suggest that early sudden improvements have a lasting effect and appear in most patients receiving medication. Clinical guidelines influenced by these contradictory findings are mixed and confusing.

Objective: To evaluate the occurrence and effects of abrupt improvements in symptoms in placebo vs antidepressant conditions in individuals with late-life depression, using a rigorous method of identifying sudden gains, developed and tested in scores of studies in psychotherapy research.

Methods: We analyzed data (collected during 1999–2002) from 174 patients 75 years or older, with unipolar depression (based on *DSM-IV*), who were randomly assigned to citalopram or placebo. We tested differences between conditions in the prevalence of sudden gains, and their effect on outcome, using χ^2 analyses and linear regression models. Pretreatment predictors of sudden gains were identified using a machine learning approach.

Results: 36.2% of patients showed stable sudden gains, without significant differences between medication and placebo conditions ($\chi^2_1 = 0.95$, $P = .33$). The mean reduction in the Hamilton Depression Rating Scale score was 7.2 points greater for patients who showed sudden gains ($t_{172} = -7.52$, $P < .0001$). Higher levels of pretreatment symptom severity and higher processing speed increased the likelihood of showing sudden gains.

Conclusion: Even in a geriatric population, which is likely to show more sustained depression and less fluctuation, sudden gains were common. The findings may necessitate modifying current models of mechanisms of change of antidepressant medication and may affect guidelines for best clinical practice.

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According to the prevailing model describing the therapeutic action of antidepressant medication, therapeutic effects appear gradually, over a period of several weeks.[1] Most cogently articulated by Quitkin and colleagues[1–3] in a series of well-known papers, the gradual/delayed model of antidepressant effects holds that "true drug" effects tend to be incremental and occur later in the course of a clinical trial (ie, after week 4) and, once achieved, tend to persist. In contrast, "abrupt improvements" occur early in the course of a clinical trial, tend to be transient, and are more characteristic of a placebo pattern of response. To the extent that this formulation is accepted, researchers focus mechanistic investigations on biological processes occurring on a delayed time scale (eg, synaptic plasticity), and clinicians educate their patients that lasting symptomatic improvement takes weeks to manifest.

Given its persistence over 4 decades, it is notable that nearly all subsequent analyses of pharmacotherapy data have failed to support the gradual/delayed model of antidepressant effects.[4] Early improvement, such as within the first 2 to 4 weeks of treatment, frequently occurs in drug trials, and it has been consistently identified as a predictor of symptom response and remission at study endpoint.[5,6] In recognition of this fact, both research and clinical practices have shifted toward switch or augmentation strategies when no significant clinical improvement is noted by week 3 or 4 of a new medication trial.[7] Moreover, multiple meta-analyses of clinical trial data have reported similar time courses of response between medication- and placebo-treated patients.[8]

In parallel with the increasing recognition of the therapeutic value of abrupt improvements in pharmacotherapy trials, interest in sudden gains occurring in psychotherapy studies has burgeoned. In a study of cognitive behavioral therapy for depression, Tang and DeRubeis[9] found that more than half of the total improvement in many patients was concentrated in 1 between-sessions interval. Many of these changes were found to be large and long-lasting, leading the investigators to suggest that sudden gains captured an important process in the patients' improvement. Subsequent meta-analyses[10] suggested that sudden gains are prevalent and signify a positive development in treatment, resulting in good outcomes, even when occurring early in treatment. Not only were sudden gains found to predict significantly better outcomes at the end of treatment, but patients who experienced sudden gains were significantly less depressed 18 months post-therapy than were those who did not experience sudden gains.[9,11,12]

Clinical Points

- Clinical practice and models of mechanisms of change after initiation of antidepressant therapy are based on delayed gradual linear improvements, but the present findings suggest otherwise.
- When working with patients with major depressive disorder, physicians should be aware of the present finding that for a third of patients, much of the change in symptoms occurred in 1 between-sessions interval, usually in the first few weeks of treatment.

The aim of our present study was to synthesize recent pharmacotherapy and psychotherapy findings on the time course of depressive symptom response by applying the concept of sudden gains to data from an antidepressant clinical trial. We hypothesized that sudden gains, rather than representing a treatment modality–specific pattern of response or transit response, may be a general phenomenon occurring in depressed patients responding to a variety of treatments (ie, psychotherapy, medication, or placebo) across age populations. Given that nearly all of the above-cited work was conducted in young or middle-aged patients, we sought to determine whether sudden gains also occurred in patients with late-life depression, an illness that is more chronic, recurrent, and treatment-resistant than depression occurring in younger adults[13] and that is therefore less likely to show spontaneous recovery. If so, such findings, when integrated with the available literature, may serve as a robust demonstration of the sudden gains phenomenon as one path of change in successful treatments, common across treatment modalities and age populations. Thus, using data from a large, rigorously conducted clinical trial of citalopram versus placebo for the treatment of older adults with major depressive disorder, we evaluated the predictors of sudden gains and their time course and persistence in the antidepressant medication and placebo conditions. We hypothesized that early, abrupt improvements would be common in older depressed patients, would predict positive treatment responses at study endpoint, and would occur at similar rates in both drug- and placebo-treated patients.

METHODS

Sample and Clinical Trial Procedures

The procedures used in this multisite, placebo-controlled trial have been described previously[14] and were approved by all the relevant institutional review boards. Briefly, during the years 1999–2002, 174 community-dwelling men and women 75 years or older, who met *DSM-IV* criteria (based on a structured clinical interview) for nonpsychotic unipolar depression (single or recurrent), with a baseline 24-item Hamilton Depression Rating Scale (HDRS)[15] score ≥ 20, participated in this 8-week randomized controlled trial. All patients began the trial with a 1-week, single-blind placebo lead-in. The baseline visit was conducted at the end of the lead-in period. At 15 centers, patients were randomized to citalopram (20 mg/d) or matched placebo at a ratio of 1:1 if they continued to meet inclusion criteria at the end of the placebo lead-in period. At the end of the fourth week, patients with an HDRS score > 10 had their medication dose increased to 2 pills per day, ie, 40 mg of citalopram or 2 placebo pills. Clinical assessments were conducted at baseline and at weeks 1, 2, 3, 4, 5, 6, and 8 (final week). Consistent with previous publications of these data, weekly assessments of the HDRS were used as the treatment outcome variable. Clinical response was defined as reduction in HDRS or in Clinical Global Severity Impression (CGI)[16] scores of 50% or more at the final assessment.

Definition of Sudden Gains

Consistent with previous literature,[9] the following definition of sudden gains was used in the present study:

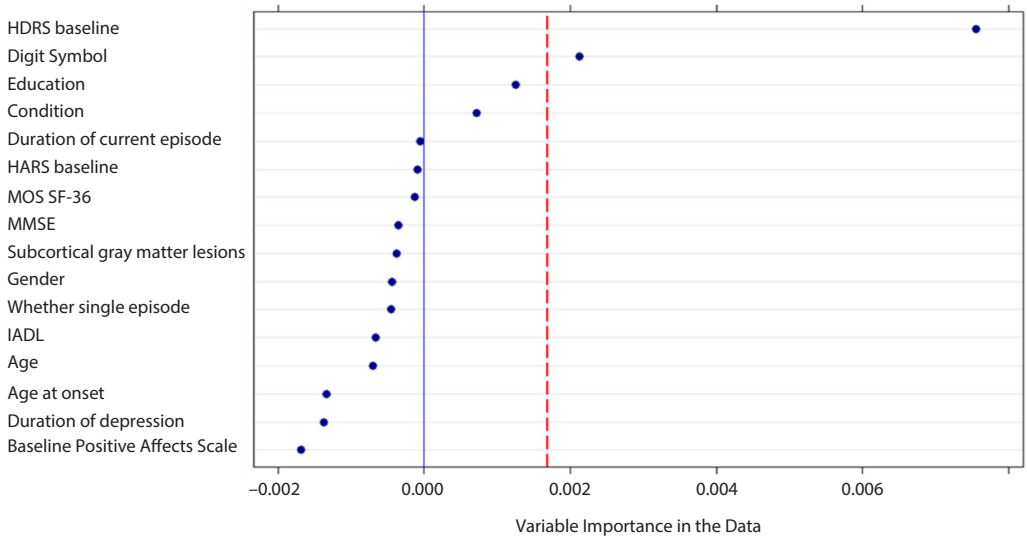
1. The gain between 2 consecutive sessions must be at least 7.74 points on the HDRS, which represents the reliable change index.[17]
2. The gain must be large relative to pregain severity, ie, at least 25% of the HDRS score of the pregain session.
3. The gain must be large relative to symptom fluctuation before and after the gain. In other words, based on Tang and DeRubeis,[9] the difference between the mean HDRS score of the 3 sessions before the gain ($n-2$, $n-1$, and n) and of the 3 sessions after the gain ($n+1$, $n+2$, and $n+3$) is at least 2.78 times greater than the pooled standard deviations of these 2 groups of HDRS scores. In view of previous reports of gains in the second week of treatment,[8] baseline HDRS score was also used to allow detection of sudden gains as early as the second session. When gains occur at the second session or at the second to last session, $n-2$ and $n+3$ are not used. When gains occur after the first session, 50% of the gain must be maintained for 2 sessions.

The first criterion refers to the question whether the gain was large in absolute magnitude, whereas the second criterion refers to the question whether the gain was large relative to the individual patient's HDRS severity at the pre-gain session. A priori analyses focused on sudden gains, which by definition met all 3 of the above criteria. For exploratory analyses, we also distinguished instances of improvement meeting the first 2 criteria, which we termed "stable and unstable sudden gains."

Statistical Analyses

To identify the patients most likely to show sudden gains on the basis of their pretreatment characteristics, we used the bootstrap aggregation of model-based recursive partitioning with the random forest algorithm, as implemented in the R package "mobForest" (version 1.2).[18] In this method, 800 model-based trees (ie, pathways for determining which

Figure 1. Variable-Importance Plot Predicting Sudden Gains[a]



[a]The horizontal axis represents the average increase in classification accuracy gained by using the given variable in the "real" data compared to permuted (ie, "mixed up" or fake) data. The solid vertical line in the variable-importance plot represents the value of 0 on the x-axis. Positive values (to the right of the solid line) indicate that a variable not only predicts sudden gains, but also performs better than random noise. The dashed line represents the random noise of all potential predictors and is constructed using the absolute value of the worst predictor.

Abbreviations: HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale, IADL = Instrumental Activities of Daily Living (intake assessment), MMSE = Mini-Mental State Examination, MOS SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey.

variables best predict sudden gains) were constructed based on bootstrapped samples from the primary dataset. For each tree, the model-based recursive partitioning method searched for binary splits in the sample, resulting in model parameters that on one side of the split are most different from those on the other side. We used a random sample of partitioning variables for splitting at each node (ie, potential split-point). Final model predictions were obtained by aggregation across the trees. The minimum α level for splits was set to 0.05, and the minimum leaf size for splitting was set to 30 patients. All relevant clinical, demographic, neurocognitive, and functional data collected in the study at baseline were investigated as potential predictors in the mobForest model, resulting in a total of 16 variables. Although the bootstrapped scheme is exploratory, using it to select variables yields stable predictors, less sensitive to the unique features of a given data set.

To examine our hypotheses, we first tested the assumption that abrupt improvements are transient by calculating the percentage of patients showing sudden gains (eg, abrupt improvements fulfilling all 3 of the above criteria). Second, we used the log rank test to examine whether sudden gains occurred earlier in the placebo than in the medication group. Third, we investigated whether sudden gains occurred more in the placebo group than in the medication group (using χ^2 test for independence) and whether sudden gains had any effect on outcome (using *t* tests). We also examined whether treatment condition moderated the association between gains and outcome and whether sudden gains had a greater effect on outcome in the placebo than in the medication group, using a linear regression, including an interaction between the occurrence of gain and treatment condition, controlling for the main effects, to predict changes in HDRS score from pre- to post-treatment.

RESULTS

Clinical and Demographic Characteristics of Participants and Clinical Trial Results

Eighty-four patients were randomized to citalopram and 90 to placebo. Fifty-eight percent of participants were women, mean age was 79.6 years (SD = 4.4), and the mean baseline HDRS score was 24.3 (SD = 4.1). The remission rate, defined as a final HDRS score < 10, was 35% for the citalopram group and 33% for the placebo group. Type of treatment did not significantly predict treatment outcome.[14]

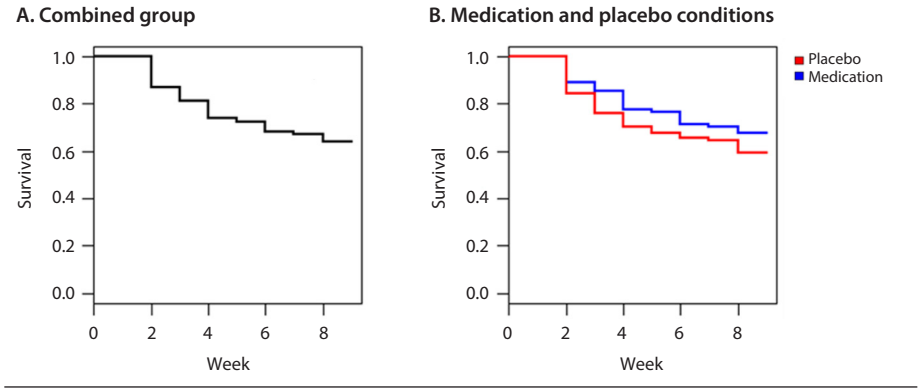
Patient-Level Predictors of Sudden Gains

The bootstrap aggregation of model-based recursive partitioning by the random forest algorithm revealed that patients with more severe symptoms and higher processing speed (as assessed using the WAIS-III Digit Symbol Subtest)[19] at baseline were most likely to show sudden gains (Figure 1).

Prevalence and Time Course of Sudden Gains

Sudden gains were observed in 36.2% of the patients. Of the symptom changes meeting criteria 1 and 2 defined above, 74.1% (63 out of the 85 total observations that met the first 2 criteria) also met criterion 3 to qualify as

Figure 2. Time to First Sudden Gains (A) in the Combined Group and (B) Separately for Each Condition



sudden gains (ie, as opposed to unstable sudden gains, which represented only 25.9% of these improvements). Sudden gains were not evenly distributed across the course of treatment ($\chi^2_7 = 432.5$, $P < .0001$). Of the 63 total sudden gains observed, 23 occurred at week 2 (34.3%), 11 at week 3 (16.4%), and 12 at week 4 (17.9%), so that in total, 68.7% occurred in the first 4 weeks. As shown by a nonsignificant log rank test (Wald statistic = 1.41, $P = .23$), sudden gains did not occur significantly earlier or later in the placebo group than in medicine-treated patients (Figure 2). Twenty-nine of 90 (32.2%) patients receiving placebo showed sudden gains, compared with 34 of 84 (40.5%) patients in the medication group. There were no significant differences between the occurrence of sudden gains between the 2 conditions ($\chi^2_1 = 0.95$, $P = .33$).

Associations Between Sudden Gains and Therapeutic Outcome at Endpoint

Patients showing sudden gains were significantly more likely to show better treatment outcome, as defined by changes in HDRS from pre- to post-treatment ($t_{172} = -7.52$, $P < .0001$). This finding remained significant even after controlling for baseline depression severity and processing speed ($F_{166,1} = 49.1$, $P < .0001$). The mean reduction in HDRS was 14.8 (SD = 7.4) for patients showing sudden gains vs 7.6 (SD = 6.6) for those not showing sudden gains. A similar pattern of results was manifest when both stable and unstable sudden gains were included in the analysis, and abrupt improvements, regardless of persistence, were associated with significantly greater changes in HDRS from pre- to posttreatment ($t_{172} = 4.467$, $P < .0001$); the mean reduction in HDRS was 12.2 (SD = 8.3) for patients showing abrupt improvements (both stable and unstable) and 7.05 (SD = 6.7) for those not showing abrupt improvements.

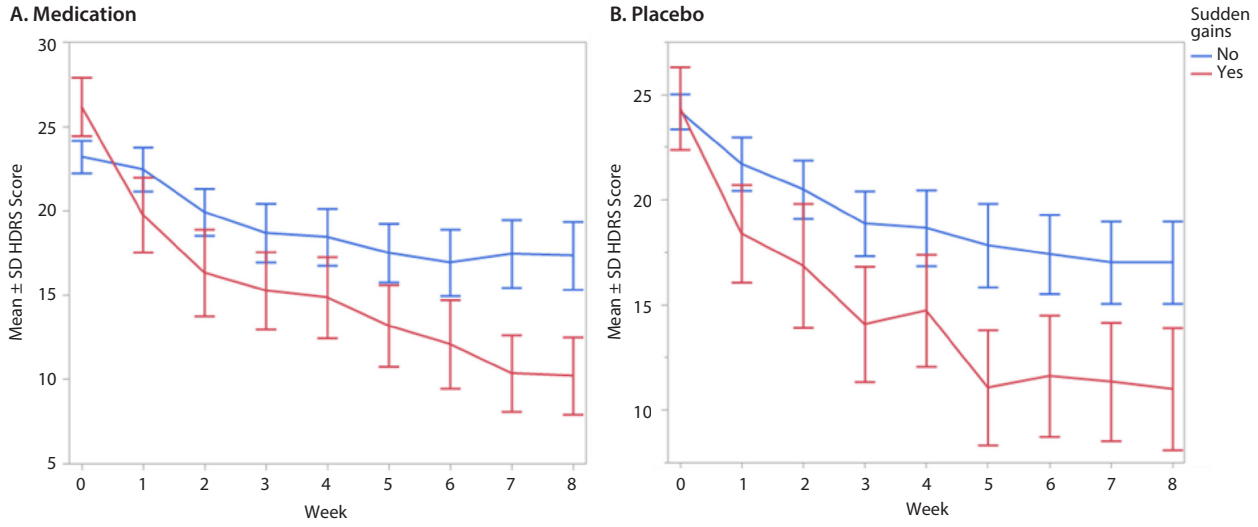
Next, we examined whether treatment condition moderated the association between improvements and outcome, such that sudden gains had a greater effect on outcome in the placebo than in the medication group. Findings suggest a trend toward a significant interaction between treatment condition and the presence of stable sudden gains ($B = 3.93$, SE = 2.17, $t = 1.80$, $P = .07$; see Figure 3). Post hoc tests showed that the magnitude of the effect of sudden gains on outcome was moderately greater in the medication condition ($B = 10.11$, SE = 1.53, $t = 6.61$, $P < .0001$) than in the placebo condition ($B = 6.18$, SE = 1.55, $t = 3.98$, $P = .0001$). Note that this interaction became significant when unstable sudden gains were included in the analysis ($B = 5.07$, SE = 2.26, $t = 2.24$, $P = .02$), so that the effect of stable and unstable sudden gains on outcome was significantly greater in the medication condition ($B = 7.68$, SE = 1.53, $t = 4.72$, $P < .0001$) than in the placebo condition ($B = 2.61$, SE = 1.57, $t = 1.65$, $P = .10$).

Sudden gains were significantly associated with responder status ($\chi^2_1 = 31.57$, $P < .0001$), with individuals experiencing sudden gains having a 66.7% chance of being treatment responders, whereas 76.6% of those not experiencing sudden gains were nonresponders. Because both sudden gains and treatment response were calculated based on HDRS scores, we repeated the categorical analyses using CGI improvement scores. Similar findings were observed: sudden gains were significantly associated with responder status ($\chi^2_1 = 38.39$, $P < .0001$); 74.6% of individuals experiencing sudden gains were responders, compared to 73.9% of those not experiencing sudden gains who were nonresponders.

DISCUSSION

Contrary to the tenets of the gradual/delayed model of antidepressant action, but consistent with the psychotherapy literature on sudden gains, we found that more than a third of patients in the antidepressant clinical trial analyzed showed stable sudden gains, which greatly outnumbered unstable sudden gains experienced by study participants. Sudden gains occurred most often in the first 4 weeks of treatment, especially in the second week, without significant differences between the medication and placebo conditions in their time or probability of appearance. This is consistent with the finding that in 91% of randomized controlled trials, 50% or more of the overall reduction in HDRS scores occurs during the first 2 weeks of treatment.[8] Sudden gains (whether stable or unstable) were even better indicators of successful treatment in the medication than in the placebo

Figure 3. Mean HDRS Scores Across Treatment for Patients in the Medication and the Placebo Conditions Showing Sudden Gains vs Not Showing Sudden Gains



Abbreviation: HDRS = Hamilton Depression Rating Scale.

condition, in stark opposition to older models of "true drug" vs placebo patterns of response. Furthermore, sudden gains were found to be affected by some of the variables that have been known to be associated with effective treatment for depression in general, and for late life depression in particular[20,21]: symptom severity and processing speed. More severe symptoms and higher processing speed were found to indicate greater likelihood of showing symptom reduction in the pattern of sudden gains. The ability of processing speed to predict sudden gains may be a spurious association, namely, a product of the association between sudden gains and processing speed on one hand and good outcome on the other.[20,21] An alternative explanation is that high processing speed may indicate an intact cognitive capacity that may provide the individual the needed flexibility that is theorized to enable building on initial change to demonstrate further change[22,23] and thus demonstrate an upward spiral process that is theorized to be the critical mechanism underlying the effects of sudden gains.[9]

The high prevalence and therapeutic significance of sudden gains across psychopharmacologic and psychotherapeutic treatment modalities suggest that sudden gains may be characteristic of any successful treatment of depression in general. The current findings are an especially robust demonstration of that because the mean age of the present sample was 79.6 years. This population is generally characterized by chronic, recurrent depression, with accompanying age-related brain changes (eg, hippocampal atrophy, declining dopaminergic function, cerebrovascular disease), with as many as 50% of adults treated for late life depression failing to respond to pharmacologic therapy.[24–26] These facts notwithstanding, in the present analysis, individuals experiencing sudden gains had a 66.7% chance of becoming responders by the end of treatment (74.6% based on the CGI). Thus, even in a geriatric population that generally shows more sustained depression and less fluctuation than do younger individuals, so that spontaneous recovery is less common, patterns of sudden gains that have been identified in younger populations were prevalent and had a profound effect on outcome.

The viewpoint one adopts on the therapeutic utility and meaning of abrupt improvements has far-reaching consequences for both clinical practice and research on mechanisms of therapeutic action. Clinicians who consider sudden gains to be critical for achieving change in many patients may modify their psychoeducational strategies in day-to-day clinical practice. For example, instructing patients that any abrupt symptomatic improvements are unlikely to benefit them in the long term may serve as a well-meaning but ultimately false and self-fulfilling prophecy. Accurate information about early improvement being a positive sign that increases the likelihood of response and remission may enhance patient expectancy of improvement and synergistically improve outcomes. Similarly, research on the mechanisms of action of serotonergic antidepressants has been guided by the idea that drug response is delayed, leading investigators to focus, for example, on later-developing synaptic plasticity, rather than on the immediate consequences of serotonin reuptake inhibition.

An important implication of the study results has to do with the proper time course of symptom assessments in antidepressant clinical trials and studies of depression in general. It is unclear, for example, whether sudden gains are rapidly occurring, epiphanic phenomena or whether they occur gradually in the course of the week, between typical study assessments in a clinical trial. It is reasonable to speculate as a potential underlying mechanism that when depressed patients begin to improve, they may increase

their activities (gradual change), which may result in more opportunities for adaptive interactions with others, which in turn may trigger an escalating change, resulting in a large gain for that week. Experiencing a sudden gain may validate earlier expectations to feel better and foster further commitment to change and medication compliance. This interpretation is consistent with Tang and DeRubeis'[9] upward spiral hypothesis and with the suggestion by Hayes et al[22,23] that early change may increase flexibility and facilitate later processing. Although in psychotherapy sudden gains appear even when assessments are made twice a week,[9] fine-grained data incorporating momentary assessments of depressive symptoms are needed.

Main limitations of the study are the sample size and the measures used. As in most of the literature on sudden gains, we used the same measure (HDRS) to define sudden gains and treatment outcome. Although we have good reasons to believe that the findings will be replicated using other measures because our analyses demonstrated even stronger results using the CGI, future studies should test this issue further. Future studies should also replicate the present findings with younger populations, especially in trials that show significant differences between antidepressant medication and placebo.

In sum, the analyses presented here reveal how little we know about the process of symptom change in patients receiving antidepressant medication. Clinical practice and models of mechanisms of change are based on delayed linear gradual improvements, but recent data suggest otherwise. For a third of patients, much of the change in symptoms occurred in 1 between-sessions interval, usually within the first few weeks of treatment. These findings should motivate increased attention to the time course of symptom response in depression studies, using novel assessment methodologies able to capture change on fine-grained time scales.

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