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Adherence to escitalopram treatment in depression: a study of electronically compiled dosing histories in the 'Depression: the search for phenotypes' study

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Abstract

Poor adherence to depression treatment is common. Understanding determinants of poor adherence to therapy is crucial to ensure optimal clinical outcomes. The aim of this study was to describe characteristics of dosing history in participants with depression receiving once daily escitalopram. Participants were randomly assigned to interpersonal psychotherapy (IPT) or pharmacotherapy. Participants assigned to IPT who did not evidence a response or remission had escitalopram added to their treatment. Adherence to pharmacotherapy was assessed using an

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Alette M. Wessels: detailed analysis of the adherence patterns, fastidious evaluation of the data patient by patient to ensure key indicators were adequately captured across three different databases associated with the study. Lead author in writing the manuscript. Yuyan Jin: analysis of adherence patterns, discussions on adequately capturing issues relating to ascertainment bias in the extraction of this information, Bruce G. Pollock: design of study, writing of manuscript, Ellen Frank: design of study, implementation of the adherence monitoring, close review of the analyses relating to adherence patterns, and writing of manuscript, Anne-Catherine Lange: analysis of adherence patterns and generation of unique visualizations for within-individual adherence patterns, writing of manuscript, Bernard Vrijens: analysis of adherence patterns, advising on the implementation of the adherence monitoring in this study design, evaluation of the adherence data as the study was ongoing, and development of novel visualization techniques for this high dimensional data, Andrea Fagiolini: execution of the clinical study, implementation of the adherence measures during the study including coordinating with study personnel to ensure adequately capture of key data, manuscript writing, David J. Kupfer: design and analysis of the overall study design, important input on the analysis techniques as well as manuscript revisions, Paola Rucci: involved in data collection and analysis as well as coordinating with this; contribution to manuscript revisions, Gail Kepple: key individual who coordinated the collection of the adherence data, providing this in real time for quality control checks and also contributing to design/protocol modifications necessary to ensure that the information was adequately captured. Review of final analysis and manuscript information with input into manuscript revisions, Joel Anderton: key contributions in coordinating datasets with multiple factors that were necessary for the advanced adherence analysis as well as for minimizing ascertainment bias – contribution to manuscript revisions, Joan Buttenfield: key contributions in coordinating datasets with multiple factors that were necessary for the advanced adherence analysis as well as for minimizing ascertainment bias – contribution to manuscript revisions, Robert R. Bies: involved with initial implementation of the adherence monitoring (in consultation with Bernard Vrijens, John Urquhart, Ellen Frank, Bruce G. Pollock and Andrea Fagiolini) as well as continued evaluation of the data as it was being collected. Oversaw the advanced analyses of the adherence patterns and contributed to the writing of the manuscript.

Conflicts of interest

There are no conflicts of interest.

electronically monitored pill cap (MEMS). Fifty-four participants on escitalopram alone and 32 on escitalopram + IPT were monitored. After 200 days, 71.7% of the participants in the escitalopram group and 54.8% of those in the escitalopram + IPT group were still engaged with the dosing regimen. Of those engaged in the dosing regimen, 17.9% (average over 210 days) of the participants did not take their medication (nonexecution). In 69% of the days participants took the correct dosage required. On average, participants had three drug holidays and the mean length of a holiday was 7 days per patient. No difference in adherence patterns was observed between patients receiving escitalopram alone vs. IPT+ escitalopram. Early discontinuation of treatment and suboptimal daily execution of the prescribed regimen are the most common facets of poor adherence in this study population.

Keywords

adherence; depression; MEMS

Introduction

Despite increasing accessibility to adequate pharmacological or psychotherapeutic treatments, depressive disorders are still associated with high rates of relapse and recurrence during a patient's lifetime. One of the reasons for these relapses/recurrence is poor adherence to prescribed medication therapy (Melfi *et al.*, 1998). Nonadherence to depression treatment is common with estimates ranging from 40 to 75% (Pampallona *et al.*, 2002). Although nonadherence is problematic throughout the treatment course, the early phase of treatment is a particularly critical period with an increased risk of treatment dropout, medication discontinuation (Sirey *et al.*, 2001a, 2001b), and vulnerability to suicide (Valenstein *et al.*, 2009). Younger age, comorbid alcohol or other substance abuse, comorbid cardiovascular/metabolic conditions, use of older generation antidepressants, and residence in lower-income neighborhoods were associated with lower acute-phase adherence (Akincigil *et al.*, 2007).

Methods for measuring medication adherence vary in important ways that might influence the validity of the conclusions yielded using differing assessment methods. Electronic dose monitoring devices have been regarded as the best available adherence measures (Chesney, 2006), and although not a perfect measure of medication adherence, studies have shown that electronic monitoring devices are more accurate than pill counts or self-report, both of which appear to significantly overestimate adherence rates (O'Brien *et al.*, 1992; Stephenson *et al.*, 1993; Burney *et al.*, 1996; Liu *et al.*, 2001). The most widely used electronic monitoring device is the medication event monitoring system (MEMS). MEMS caps use a computer chip that is embedded in the top of the pill bottle that automatically records the date, time, and duration of pill bottle opening. The device is simple and easy to use, and does not rely on retrospective recall of medication use, therefore giving 'objective' adherence data. The aim of this study was to describe characteristics of dosing history in participants with depression receiving once daily escitalopram, using data of a carefully monitored, cross-national depression treatment trial (Frank *et al.*, 2008, 2011). As this is a descriptive study, no formal hypotheses are tested. A key aspect of this study was to highlight the significant intraindividual variability in the execution of a prescribed drug regimen in adult depressed patients receiving escitalopram.

Experimental procedures

Participants in this study were part of the study 'Depression: the search for phenotypes', a clinical multisite trial (Department of Psychiatry of the Universities of Pittsburgh, USA and

Pisa, Italy) conducted to determine the mediators and moderators of treatment response in major depression. Its research design and methods have been described previously (Frank *et al.*, 2008, 2011) (http://clinicaltrials.gov/ct/show/NCT00073697). MEMS recordings were available for the Pittsburgh site only and therefore the analysis and results presented in this paper will be limited to the data obtained from the Pittsburgh site.

For the initial (acute) phase of treatment, participants were randomly assigned to treatment with the selective serotonin reuptake inhibitor (SSRI), escitalopram (dose: 20 mg/day), or with interpersonal psychotherapy (IPT). Study medication was prescribed each week. Patients in the IPT treatment arm met weekly with their IPT therapist for ~45–50 min, during the first 16 weeks of treatment. All patients who had responded [50% reduction in baseline score on the Hamilton Rating Scale for Depression (HRS-D); Hamilton, 1967] at 8 weeks and evidenced a remission (mean HRS-D ≤ 7 × 3 weeks) at 16 weeks, had IPT sessions at 18 and 20 weeks and then moved on to monthly IPT continuation treatment. Patients entering the continuation phase were seen every other week for the first month and then once a month for the remainder of the 6-month continuation phase.

Participants who did not meet response criteria [defined as a 50% reduction in baseline (HRS-D)] after 6 weeks of treatment had the other treatment added for an additional 6 weeks. Participants who met remission criteria (mean HRS-D ≤ 7 for 3 weeks) at the 12-week point were continued in the treatment or combination that led to their remission for an additional 6 months (the continuation phase). Participants who did not meet remission criteria at the 12-week point were offered alternative treatment.

Adherence to pharmacotherapy

Adherence to escitalopram was tracked prospectively using an electronically monitored pill cap (MEMS V; AARDEX Group Ltd., Sion, Switzerland). Each participant received a pill bottle with a cap that recorded the time and date of each opening and closing of the bottle. The monitor does not provide any reminder or timer or alarm for the patient. To maximize MEMS data accuracy, participants were instructed not to use pill organizers or take ‘pocket doses’ (e.g. removing multiple pills for later use), and to open the MEMS cap only when taking a dose.

Definitions and analysis

Adherence is a blanket term describing the extent to which patients’ drug dosing history corresponds with the prescribed drug dosing regimen. Adherence can be broken down into several components: acceptance/initiation, persistence, execution and discontinuation (Blaschke *et al.*, 2012; Vrijens *et al.*, 2012) (Fig. 1).

Acceptance refers to the action taken by the patient to initiate treatment after treatment has been prescribed (i.e. the patient started taking the medicine).

After the drug regimen has been initiated, persistence can be determined. Persistence is defined as the time elapsed (in days) between first drug intake and treatment discontinuation. If 7 days of treatment were missed consecutively, participants would be deemed nonpersistent. Persistence is computed as follows: [(discontinuation day− start day) +1].

If a patient discontinued the treatment early, persistence was considered an event on that day (status=1). A patient was considered nonpersistent when the discontinuation day occurred 7 days before the end of the follow-up period. In creating Kaplan–Meier curves, to display persistence over time, persistent patients were considered censored and nonpersistent patients were considered an event. The only patients who were actively engaged in the study

were utilized for the persistence calculations (i.e. documented absence of openings of the MEMS cap device). Thus, a patient who dropped out of the study was only considered up until the last measurement available from the MEMS device for calculation of initiation, execution, and discontinuation-based metrics.

Execution is defined as the correspondence between the patient's actual dosing history and the prescribed dosing regimen. The execution pattern was summarized in a sequence of binary data Z_{ij} indicating whether yes (1) or no (0), the prescribed dose was taken by patient *i* on day *j*. This coding preserves the temporal structure in the individual drug taking patterns. On each day, execution was computed as the percentage of patients that have taken the prescribed dose on that day. Openings on visit days outside the regular intake pattern and within office hours were considered openings at the doctor's appointment or openings at the pharmacy and were therefore removed from the MEMS output file.

The nature of each opening was identified as follows: 0: regular sequence; 1: drug holiday; 2: nondrug holiday (equipment failure, MEMS cap in the lab/pharmacy, patient indicated loss or issue with MEMS cap); 3: lost to follow-up.

A missed dose was defined as no redosing within 24 h from the previous dose. A drug holiday is defined as a period of at least 3 consecutive days (>72 h) without dose intake.

Within the execution phase of adherence to the prescribed dosage regimen, multiple summary statistics can be calculated to evaluate group characteristics. These summary statistics include: correct dosing, taking adherence, and timing adherence.

The percentage of prescribed number of doses taken (taking adherence) was calculated as

$$\frac{\text{Number of openings}}{\text{Number of prescribed doses}} \times 100.$$

This measure reflects both the average dose received over a given period and the total dose received over that period. However, it fails to distinguish between a patient who takes their medication regularly and a patient who balances periods of underdosing with periods of overdosing and it captures no information about the precise timing of drug intake.

The percentage of days with correct number of doses taken (correct dosing) was calculated

$$\frac{\text{Number of days with number of openings as prescribed}}{\text{Number of monitored days}} \times 100.$$

This statistic captures some measure of the closeness to 'correct adherence'. Depending on how the latter is defined, it may reflect the degree of regularity in lifestyle. However, this summary measure gives no information concerning the timing of dose intake, it does not distinguish between days of overdosing and days of underdosing and thus may not capture deviations most relevant to the drug action.

The percentage of doses taken within prescribed intervals (timing adherence) was calculated as

$$\frac{\text{Number of openings within } \pm 3 \text{ h around the prescribed}}{\text{Number of prescribed doses} - 1} \times 100.$$

This measure was introduced on the basis of periods of 'overdosing' (interval too short) and periods of 'underdosing' (interval too long). Timing adherence evaluates the number of deviations that exceed a crucial or meaningful threshold of dosing intervals that are either too short or too long.

Wilcoxon's test was used to assess the effect of the following covariates on adherence: treatment phase (acute vs. continuation), age (< 30 vs. ≥ 30), sex (male vs. female), and marital status (married vs. other).

The Institutional Review Board at each study site approved the study, and all participants provided written informed consent. The study procedures were carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000.

Results

Eighty-six participants [median age 40.5 years (range 20.4–64.7 years) were monitored (54 on escitalopram alone; 32 on escitalopram and IPT] for 12 538 days (SSRI alone group) and 6427 days (SSRI+IPT group). The average follow-up duration was 231 days (range 14–442 days) and 200 days (29–357 days) for the SSRI alone and SSRI+ IPT group, respectively. For patient demographics and treatment characteristics see Table 1.

Individual dosing history

Individual dosing history is shown in Fig. 2. This heat map shows accuracy of medication intake for each individual in the study [each horizontal bar represents a single patient and dosing history (observation period) over time (*x*-axis) is displayed].

For each individual, a chronology plot was used to visualize the dosing history. The chronology plots display the time of each dose (each opening and closing of the MEMS bottle) on a scatter plot of time of opening (24-h clock scale; *y*-axis) and dosing date (*x*-axis) (Fig. 3). An example of these plots using two example participants is shown in Fig. 3.

Dosing patterns vary significantly between the two participants as shown in Fig. 3. Participant 1 executes the dosing regimen poorly. A long drug holiday can be observed after ~23 days of dosing. The patient occasionally missed a dose but also overdosed on some days. Patient 2 was persistent throughout the observation period, but overdosed on many occasions (escitalopram was instructed to be dosed once daily) probably to make up for many missed doses.

Persistence

Figure 4 shows the persistence pattern. The persistence line represents the decline of the percentage of participants still engaged in the dosing regimen. After ~200 days, almost a third of the participants who were prescribed escitalopram have stopped taking the treatment. The proportion of participants still engaged with the dosing regimen after 200 days was 71.7% for participants in the SSRI group and 54.8% for those in the SSRI+IPT group. The group effect was found to be statistically nonsignificant (log-rank test; *P*-value: 0.315).

Execution

Of those engaged in the dosing regimen, 17.9% (average over 210 days) of the participants did not take their medication (nonexecution). Figure 5 shows the execution pattern over the study duration.

No statistically significant differences in execution between participants who received SSRI alone (81.4%) vs. those who received SSRI+IPT (83.4%) were observed (GEE model; *P*-value=0.668).

Drug holidays

Sixty-nine percent of all participants experienced a drug holiday. On average, three drug holidays per patient were observed and the average length of each drug holiday was 7 days (95% confidence interval: 4.9; 8.6).

Adherence summary statistics

For 69% of the days, participants took the correct dosage required. While continuing on the medication, 77.8% of the prescribed dose was taken.

No difference in adherence patterns was observed between participants receiving SSRI alone vs. IPT+ SSRI.

Effect of covariates on adherence

The effect of treatment phase, age, sex, and marital status on adherence was tested.

A significant difference between acute and continuation phase on all three adherence statistics was observed. In the acute phase, for 76% (vs. 60% in continuation phase) of the days, participants took the correct dose required (*P*=0.0043). In the acute phase, 85% (vs. 69% in continuation phase) of the prescribed dose was taken (*P*=0.0047) and 56% (vs. 42%) of doses were taken within nominal time frame (±3 h) (*P*=0.0013).

No effect of age, sex, and marital status on adherence was observed.

Discussion

Understanding adherence to therapies is crucial in clinical practice and research studies to ensure optimal clinical outcomes and valid study results. This study shows that early discontinuation of treatment and suboptimal daily execution of the prescribed regimen is the most common facet of poor adherence. At ~200 days after initiation of treatment, almost a third of the participants who were prescribed escitalopram have stopped taking the treatment. Compared with adherence rates reported in literature, this is not an unexpected finding: a review article on medication adherence (Osterberg and Blaschke, 2005) shows that participants with a psychiatric disorder have poor persistence with medication [50% persistence in antidepressant treatment after 3 months of therapy in participants with major depression (measured by medical record review and clinical interview), 40–50% persistence in participants with schizophrenia, and only 35% for participants with bipolar disorder]. For tricyclic antidepressants and SSRIs, dropout rates are in the range of 21–33% irrespective of the drug class (Anderson and Tomenson, 1995; Montgomery and Kasper, 1995). A metaanalysis on the effects of depression on participants' adherence (DiMatteo *et al.*, 2000) shows that compared with nondepressed participants, the odds are three times greater that depressed participants will be noncompliant with medical treatment recommendations. The following explanations for this phenomenon have been proposed: feelings of hopelessness inherent to depression will interfere with and make it difficult to hold positive beliefs or expectations needed for optimal adherence; social isolation and withdrawal limit interaction with family and social networks, both important factors for treatment adherence. Lastly, depression might be associated with reductions in cognitive functioning necessary for remembering and following through with treatment recommendations.

A significant difference between acute and continuation phase on all three adherence patterns was observed (correct dosing, taking adherence, and timing adherence). This is in line with MEMS data presented byDemyttenaere *et al.* (2008). Their study to investigate the evolution in adherence during 6 months of treatment found a linear drop in adherence of 2.5% per month.

An interesting finding of the study is that in participants who are persisting on medication treatment, the execution is very consistent across the period of the study with ~80% of persisting participants taking the medication correctly on any given day. Also, adherence rates were similar between participants receiving SSRI alone and participants receiving IPT and SSRI. Although primarily focused on resolving the interpersonal problems and difficulties in carrying out social roles that are viewed as precipitating or maintaining depressive symptoms, IPT grows out of a medical model of depressive illness and includes psychoeducation about the biological basis of depression and the potential role of medication in recovery from a depressive episode. Such psychoeducation helps the patient understand the medical condition, the need for treatment, and the value of the treatment. One might therefore assume an increased adherence rate in this group; however, in the present study, participants assigned to SSRI received similar psychoeducation from their clinicians. Thus, the lack of difference is probably a function of the close contact, frequency of visits, support and the amount of psychoeducation provided to the participants in the SSRI only group. Another issue regarding the lack of difference in adherence with psychotherapy is the lack of comparability. Not all individuals were assessed in parallel (i.e. SSRI vs. IPT+SSRI groups simultaneously). Many of the IPT+SSRI patients were those that initially failed an adequate trial of IPT and the SSRI was added to treatment or failed an adequate trial of SSRI and IPT was added to treatment.

The results of this study must be interpreted within the context of its limitations. An observation from this study is that patterns of deviation from prescribed dosing regimen varied widely amongst participants. None of the tested covariates in this study explained this variability. The possible relationship between the nonadherence rate and drug regimen (dose, side-effects, etc.) could not be identified given the design of the study, but these might be factors responsible. All participants in this study were aware that their adherence was being monitored. In addition, participants had many appointments to attend with the physician in the follow-up period. This may have resulted in a greater adherence than what is usually seen in the general population and, hence, overestimation of the habitual adherence of these participants. Although considered the most reliable method available to measure adherence, electronic monitoring of medication events is still an indirect measure. A patient could open the container, but not take the drug or take a different dose than the one prescribed, or invalidate data by placing medication into another container, all factors masking true adherence.

Conclusion

Early discontinuation of treatment and observed drug holidays and suboptimal daily execution of the prescribed regimen are the most common facet of poor adherence in this study population. The shortfall in drug exposure that these dosing errors create might be a common cause of low rates of depression control and high variability in responses to antidepressant drugs.

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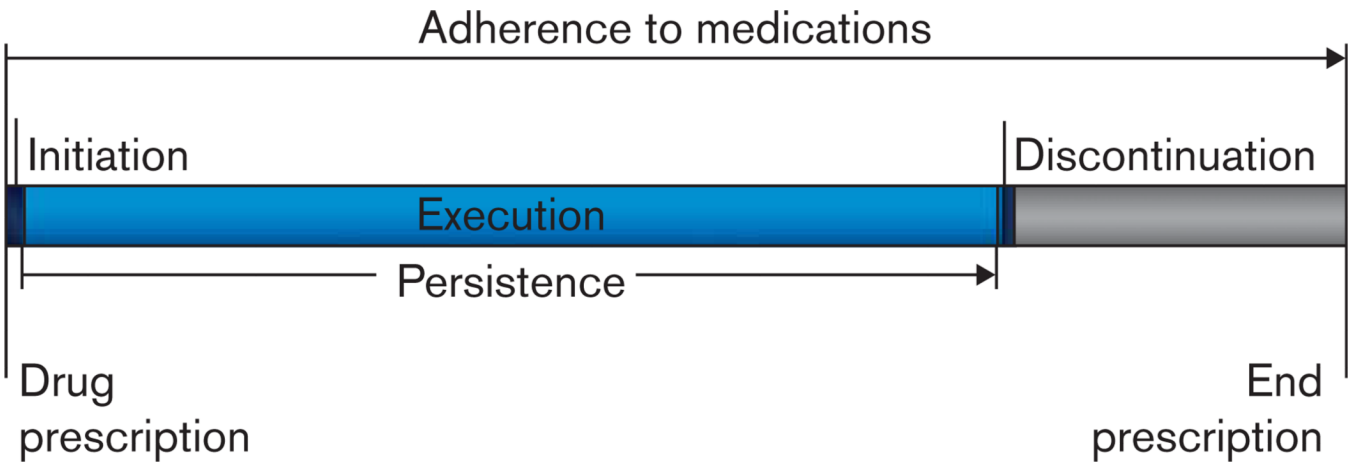

Fig. 1.
Illustration of adherence components (Urquhart and Vrijens, 2005)

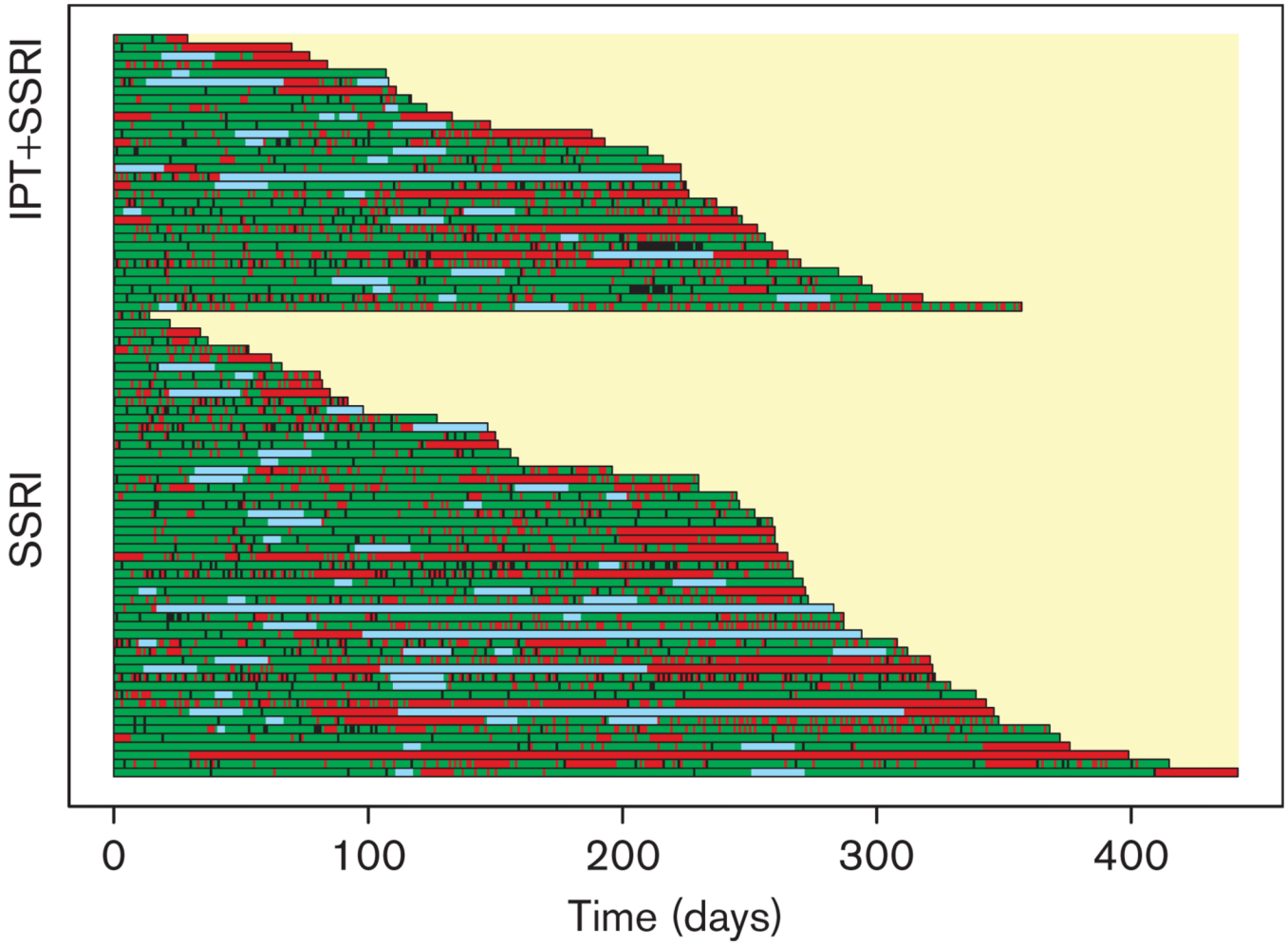

Fig. 2.

Adherence heat map; the different colors represent the following events: green: correct dose intake; red: no dose intake; black: overdosing; blue: nonmonitored. IPT, interpersonal psychotherapy; SSRI, selective serotonin reuptake inhibitor.

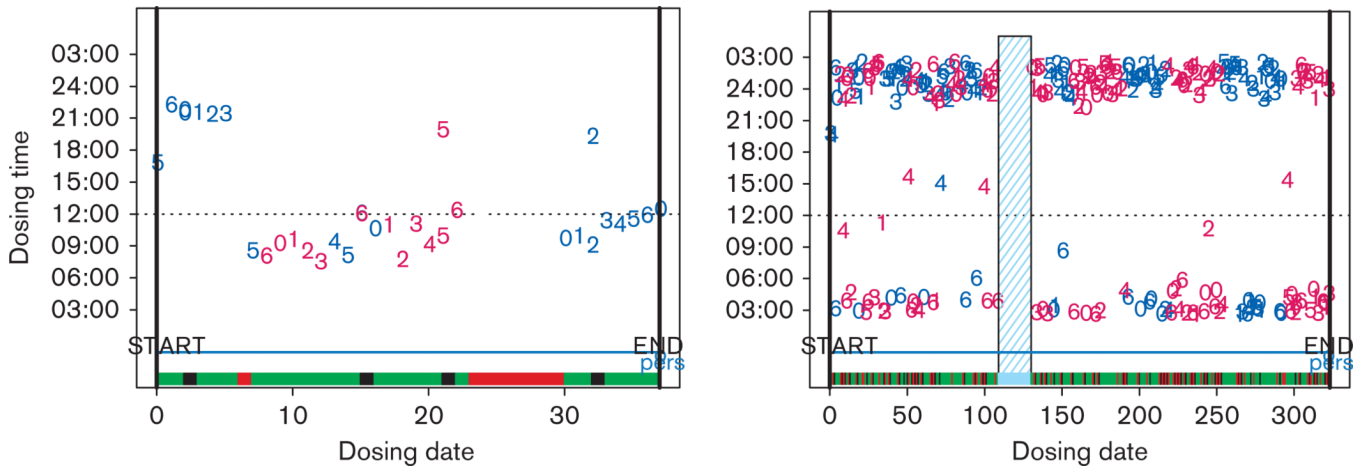

Fig. 3.

Dosing chronology plot of two participants. The horizontal axis displays the days since the randomization visit (dosing date). The vertical axis shows the time of drug intake (24 h clock; dosing time). The digits 0–6 in the figure represents the day of the week (0=Sunday, 1=Monday, …, 6=Saturday.). The black solid lines correspond to the start and the end of the monitored period. Blue shaded bars represent nonmonitored periods. The color coded band at the bottom of both plots gives a summary of the daily adherence: red is missing dose, green is correct dose; black is overdose and blue is nonmonitored.

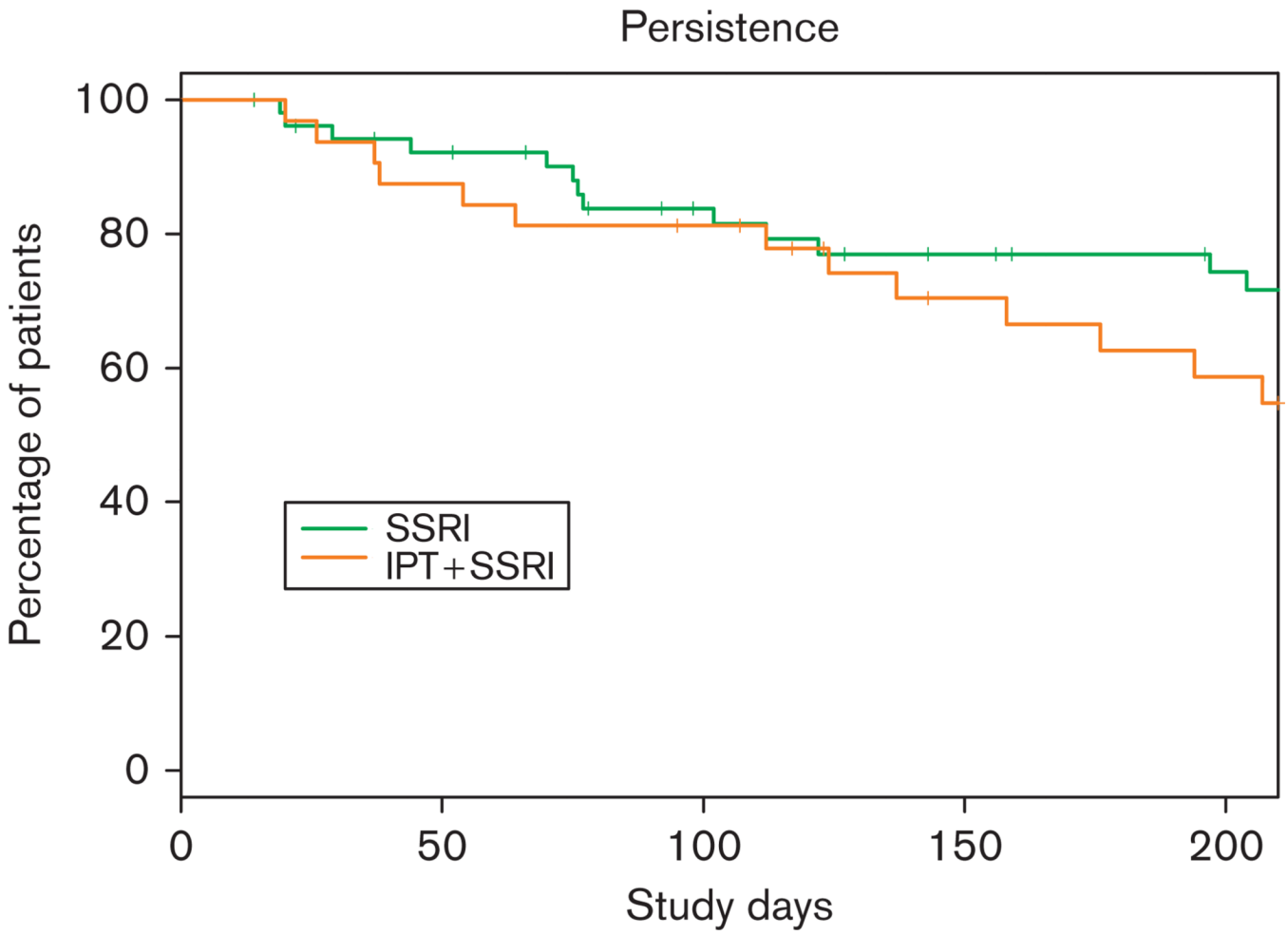

Fig. 4.
Persistence pattern. IPT, interpersonal psychotherapy; SSRI, selective serotonin reuptake inhibitor.

Fig. 5.
Execution. IPT, interpersonal psychotherapy; SSRI, selective serotonin reuptake inhibitor.

Table 1

Demographic and treatment characteristics

	N (%)	Median (range)
Sample size	86	–
Sex		
Male	40	–
Female	46	–
Age (years)	–	40.5 (20.4–64.7)
Treatment		
Acute phase	86[a]	81[b](13–231)
SSRI alone	54 (62.8)	–
SSRI + IPT	32 (37.2)	–
Continuation phase	61[a]	166[b](14–225)
SSRI alone	38 (62.3)	–
SSRI + IPT	23 (37.7)	–
Marital status		
Never married	40 (46.5)	–
Married	28 (32.6)	–
Separated	4 (4.7)	–
Divorced	12 (14)	–
Widowed	2 (2.3)	–

IPT, interpersonal psychotherapy; SSRI, selective serotonin reuptake inhibitor.

[a]Represents number of patients in the acute and continuation phase.

[b]Represents duration in days [median (range)] of acute and continuation phase.