Imipramine versus placebo for multiple functional somatic syndromes (STreSS-3): a double-blind, randomised study

Johanne L. Agger MD[1], Andreas Schröder PhD[1], Lise K. Gormsen PhD[2], J. S Jensen MSc[1], Troels S. Jensen DMSc [3], Per K. Fink DMSc[1]

[1] The Research Clinic for Functional Disorders and Psychosomatics, Aarhus University Hospital, Noerrebrogade 33, 8000 Aarhus, Denmark

[2] Psychiatric Hospital Risskov, Aarhus University Hospital, Skovagervej 2, 8240 Risskov, Denmark

[3] Danish Pain Research Center, Aarhus University Hospital, Noerrebrogade 33, 8000 Aarhus, Denmark

Corresponding author:

Dr. Johanne L. Agger

The Research Clinic for Functional Disorders and Psychosomatics,

Aarhus University Hospital,

Noerrebrogade 33, 8000 Aarhus, Denmark

Email: johanne.agger@aarhus.rm.dk

Phone: ++45-78464310 Fax: ++45-78464340

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Summary

Background

Functional somatic syndromes (FSS), e.g. chronic fatigue syndrome or irritable bowel syndrome, often co-exist. Treatment guidelines supported by high quality evidence exist for most FSS, but are lacking for multiple comorbid FSS. We aimed to assess the effect of the tricyclic antidepressant, imipramine, in patients with multiple FSS defined by the criteria for multi-organ bodily distress syndrome (BDS): a unifying diagnosis that encompasses most FSS and somatoform disorders.

Methods

In a single-centre, randomised, double-blind trial (ClinicalTrials.gov: NCT01518634) conducted in a Danish university hospital setting, consecutively referred patients (aged 20-50 years) fulfilling criteria for multi-organ BDS with no concurrent comorbid depression or anxiety disorder were randomised to either 10 weeks of low-dose imipramine or placebo (daily doses of 25-75 mg p.o.). The hospital pharmacy handled randomisation (computer-generated) and masking, providing sequentially numbered packs of study drug that were administered serially to the participants. All others involved were masked to allocation. Primary outcome was patient-rated overall health improvement on a 5-point clinical global improvement scale. Improvement was defined as patients responding "better" or "much better" as opposed to "unchanged" and "worse" or "much worse" when rating their overall health status after 10 weeks of minimum 25 mg study drug. Analyses included patients who received at least one dose of study drug.

Findings

Between January 30, 2012 and November 24, 2014, 138 patients were randomised: 70 to imipramine, 68 to placebo. The study was completed on May 1, 2015.125 patients received at least one dose of study drug: 65 received imipramine and 60 placebo. Treatment was terminated prematurely for eight (12·3%) patients receiving imipramine and seven (11·7%) patients receiving placebo. Data were missing for two (3·1%) patients receiving imipramine and three (5·0%) patients receiving placebo. Of the 120 patients (96·0%) who provided primary outcome data, 33 (53·2%) receiving imipramine reported their overall health status as "better" or "much better", whereas this was the case for 14 patients (24·6%) receiving placebo. The improvement after imipramine was significantly greater than after placebo with an OR of 3·3 (95% CI 1·6-6·8); p<0·001. NNT was 3·6

(95% CI 2·3-8·9). Analysis of the worst-case scenario for patients with missing outcome did not change the interpretation of the results. Adverse events (at least moderate intensity) were experienced by 36 (55·4%) receiving imipramine and 12 (20·0%) receiving placebo (p<0·001) and caused dropout in four (6·2%) receiving imipramine and three (5·0%) receiving placebo.

Interpretation

Imipramine treatment supported by regular contacts to clinicians significantly improved overall health in patients with multiple FSS. Adverse events were more common in the imipramine group, but only rarely led to discontinuation of treatment.

Funding

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Introduction

Patients with multiple somatic symptoms not attributable to conventionally defined disease are prevalent in all medical settings. Such symptoms may inflict suffering and reduce both quality of life and work ability in the most severely affected patients. Furthermore, the patients represent a substantial socioeconomic burden to society due to high use of health care services and social benefits.[1,2]

For clinicians, these patients pose a major diagnostic and therapeutic challenge. Depending on the primary complaint and the specialist consulted, patients receive diagnoses such as chronic fatigue syndrome (CFS), irritable bowel syndrome (IBS), fibromyalgia (FM), other functional somatic syndromes (FSS), or diagnoses of somatoform disorders. Often, patients receive two or more syndrome diagnoses at the same time, and even more fulfil diagnostic criteria for multiple syndromes.[3] In cases of multiple FSS, it is unclear which FSS should guide the treatment choice. Meta-analyses and high quality trials have given rise to pharmacological treatment guidelines in some FSS, but these are lacking for multiple FSS.[4–7]

Pharmacological treatment recommendations in single FSS focus primarily on centrally acting drugs, especially antidepressants.[1] While the evidence differs across diagnoses, antidepressants are generally found to be effective and are therefore among first-line treatments in FM and IBS.[1,4,6,8,9] Newer drugs such as serotonin–norepinephrine reuptake inhibitors (SNRIs) are increasingly used in FM, but despite the abundance of trials showing effects in selected aspects of FM, a large-scale,

longitudinal study showed no evidence of a clinical benefit compared with prior treatment with non-steroid anti-inflammatory drugs (NSAIDs) and the older and cheaper tricyclic antidepressants (TCAs).[10] TCA treatment has also proven beneficial in treatment of other FSS, but the use of TCAs are primarily supported by decades of clinical experience rather than by solid evidence or newer efficacy trials.[4,6,8,9,11]

Imipramine is a TCA most commonly used to treat depressive illness. Like other TCAs, imipramine possesses pain-modulating properties unrelated to its antidepressant effect. Pain relief is commonly noted earlier and at doses of 25-75 mg well below the effective antidepressant doses (100-200 mg), as shown especially in studies of neuropatic pain.[12]After uptake, imipramine is partially converted to an active metabolite, desipramine. Together, imipramine and desipramine cause a balanced inhibition of serotonin and noradrenaline reuptake. Adverse events are common, but the registered frequency of sedation and weight gain is lower than for amitriptyline, the most commonly used TCA. Owing to its balanced inhibition and the safety profile, imipramine may represent an easily available, affordable, and possibly beneficial treatment option for patients with multiple FSS. Besides pain relief, it may also relieve other somatic symptoms. An effective intervention for patients with multiple FSS can potentially have a large public health impact.

An evaluation of treatment across specific FSS diagnoses is facilitated with a joint diagnostic approach to the group of patients with multiple functional somatic symptoms. The recently introduced unifying research diagnosis of bodily distress syndrome (BDS) embodies this broader concept of classification as it encompasses the majority of the FSS and somatoform disorders, though recognizing a number of subtypes.[13,14] The BDS diagnosis offers a set of precise and reproducible diagnostic criteria, which have been included in the current draft of the World Health Organization's International Classification of Diseases, 11th Revision for primary healthcare.[15] Multi-organ BDS, the most severe subtype, is characterised by multiple, persistent bodily symptoms from several organ systems, and this subtype captures patients with multiple FSS.[13,14,16–18]

We hypothesised that low-dose imipramine would improve overall health as well as physical, mental, and social health in patients with multiple FSS as defined by the criteria for multi-organ BDS.

Methods

Study design

This single-centre, randomised, double-blind trial took place from January 2012 to May 2015 in a university hospital setting at The Research Clinic for Functional Disorders, Aarhus University Hospital, Denmark. The study was approved by The Ethics Committee of Central Denmark Region and was performed in accordance with the provisions of the Declaration of Helsinki, the International Conference on Harmonization of Good Clinical Practice guideline, and current regulatory requirements. The trial was monitored by the local Good Clinical Practice unit at Aarhus University Hospital.

The current trial, entitled Specialised Treatment for Severe Bodily Distress Syndrome-3 (STreSS-3), is part of a group of studies with the shared aim to provide evidence-based treatment options for patients with multi-organ BDS. A long-term follow-up is being planned including data on prescription medication, healthcare and indirect costs (i.e. labour market-related and health-related benefits) from public registries.

Patients

Consecutively referred patients with multiple, long-lasting symptoms were screened for eligibility. We selected patients (aged 20-50) with a diagnosis of chronic (i.e. minimum two years) multi-organ BDS, which requires functional somatic symptoms from at least three of four bodily systems, leading to moderate or severe impairment in daily living. The diagnosis was established by an MD after a thorough physical and psychological assessment including diagnostic interview (Schedules for Clinical Assessment in Neuropsychiatry), physical examination, blood test, ECG, and a close review of all medical records. Further details regarding assessment have been reported elsewhere.[18] We excluded patients with a lifetime diagnosis of psychosis, mania, or depression with psychotic symptoms (ICD-10: F20-29, F30-31, F32.3, F33.3). Patients with concurrent severe psychiatric disorder demanding treatment, e.g. current depressive episode, were also excluded. Patients undergoing concomitant treatment with antidepressants, anticonvulsants, analgesics, or other medication with pain relieving properties were excluded, unless this medication could be discontinued. Other exclusion criteria were imipramine treatment in sufficient dosage within the last year; known hypersensitivity to or intolerability of imipramine; abuse of alcohol, narcotics or drugs; physical comorbidity that would make imipramine inappropriate, including arrhythmias, epilepsy, hepatic insufficiency, etc.; insufficient contraception; pregnancy and breastfeeding, and use of medication that would interact with imipramine.

Randomisation and masking

Patients were randomly assigned (1:1) to low-dose imipramine (25-75 mg) or placebo. The randomisation code was generated by a trained, but independent employee at the hospital pharmacy at Aarhus University Hospital through a web-based system (www.randomization.com). Sealed, opaque envelopes containing the randomisation code for each patient were present at the investigator's site for emergency situations.

Coded (numbered) packs of study drug and matched placebo were produced according to the randomisation schedule by the hospital pharmacy. Capsules of 10 mg and 25 mg imipramine and matched placebo for 25 mg were provided by Takeda Pharma A/S; placebo for 10 mg was produced by the hospital pharmacy. The capsules of 10 mg imipramine along with pharmacy-produced 10 mg placebos were both over-encapsulated by the hospital pharmacy to ensure identical appearance. Patients, investigators, and all other staff involved in the conduct of the trial were blinded to treatment allocation for the duration of the study. Furthermore, treatment allocation remained blinded throughout all data analysis for all authors, except for the statistician, who was unblinded during the final analysis.

Procedures

At assessment, patients received thorough information about the diagnosis multi-organ BDS, including an introduction to a biopsychosocial approach to dealing with their symptoms. Patients were encouraged to modify their basic lifestyle with the intent to improve physical activity, sleep quality, diet, and network, and to increase awareness of stress factors and other factors contributing to an aggravation of their symptoms.

For patients taking pain medication or antidepressants, medications were slowly tapered and stopped during a pre-trial period of up to 6 weeks. All discontinuations were completed prior to a two-week wash-out period during which no pain medication was allowed. After wash-out, the patients started treatment with 10 mg imipramine or matched placebo, increasing to 25 mg after one week. Drugs and placebos were hereafter titrated to a maximum of 75 mg once daily. Depending on tolerance, dosages were maintained at this level during the remaining part of the study, or reduced if required. Total enrolment time was 19 weeks from inclusion until two weeks after the final dose of study drug. Up to eight tablets of 500 mg paracetamol were available daily as escape medication.

Assessment and treatment were carried out by specially trained clinicians (9 medical specialists). During treatment, the patients were seen at the clinic or contacted by telephone at week three, five, seven, ten and 13 after inclusion. Each visit was a 30-60-min. consultation or a telephone consultation of shorter duration with a medical specialist, who monitored compliance, harms, and effects.

The end point of the study was after 13 weeks of treatment, where the patients had received 10 weeks (10 week ±1 week) of sufficient dosage of study medication (i.e. minimum 25 mg).

Outcomes

The primary outcome was patient-rated overall health improvement on a 5-point clinical global improvement scale (CGI) at end point. Patients rated their general health as much worse, worse, unchanged, better or much better in response to the following question: ”How do you consider your health status now compared with when you first came to the clinic?” This simple scale correlates with other specific outcomes in this population, including physical functioning and symptom scores.[19,20] Additionally, it has the advantage of not being FSS-specific.

Secondary outcomes were differences between groups at endpoint adjusted for baseline scores in physical, mental, and social health assessed with Physical Component Summary (PCS), Mental Component Summary (MCS), and the individual subscales of the Short Form 36 Health Survey (SF-36). Data were scored and interpreted according to the Danish manual. Changes in symptoms of depression, anxiety, and somatisation were assessed by the 92-item Danish version of the Symptom Checklist (SCL-92). The Numeric Rating Scale (NRS-11) was used to assess severity of predominant symptoms, Whiteley-7 to measure illness worry, WHO Disability Assessment Schedule 2.0 (WHODAS 2.0) to assess disability and the BDS checklist to assess number of functional somatic symptoms (25 symptoms converted to a symptom score (0-100)).

For the secondary outcomes SCL-92 and the BDS checklist an additional intermediate measure was included at week three after the wash-out period to detect a possible deviation from baseline after discontinuation of medication before initiating the primary intervention of minimum 25 mg study drug.

Safety and compliance was assessed by clinical judgment and plasma concentration of study drug at end point. Adverse events, grade, and attribution were monitored using open questioning by the medical doctor at each visit.

All questionnaire data from the patients were obtained by a web-based programme, SurveyXact.

Statistical analysis

The power calculation was based on the CGI where the outcomes much worse, worse, unchanged, better, and much better were combined to give three outcome groupings (worse, same, or better). It was estimated that a sample size of 120 patients would be required to detect an odds ratio (OR) of 3·0 using a proportional odds model providing 87% power at the 5% significance level (2-sided).

All analyses were performed both according to the intention-to-treat population (ITT) defined as the patients who received at least one dose of the study drug, and to the population who completed the study per protocol (PP), i.e. completed the 13 weeks of treatment with 10 weeks of minimum 25 mg study drug.

Analysis of the main outcome, CGI score, was based on the three outcome groupings comparing imipramine with placebo using an unadjusted proportional odds model.[19,21] We reported as the main result the analysis based on data available in the ITT population. Worst case scenario was calculated for missing values in the ITT population, giving patients receiving placebo an outcome of "better" and patients receiving imipramine an outcome of "worse". The estimated number needed to treat (NNT) was based on the sample with available data responding "better" or "much better" in the CGI.

In the analysis of the secondary outcomes, we used a multiple linear regression model with outcomes at end point as the dependent variable and baseline scores and intervention as the independent variables, testing for interaction between groups and baseline score. The NRS-11 was calculated as the OR comparing the proportion of patients in the two groups experiencing a reduction from baseline of at least 30% in intensity of the predominant symptom.

In the secondary outcomes, data were imputed for the five patients with missing data. We used a univariate linear regression imputation method based on the asymptotic approximation of the posterior predictive distribution of the missing data as implemented in Stata 13.1. The imputation models included the following covariates: baseline value of the corresponding secondary outcome, level of impairment, number of functional somatic symptoms, and work status. Inferences from the imputed datasets were combined to obtain one estimate and similarly one standard error for the parameters of interest.

The baseline scores of the SCL-92 and the BDS checklist were compared to the intermediate measure at three weeks for each group using a paired t-test on the available data. Changes in the two groups were compared using an unpaired t-test.

Adverse events based on data from patients in the ITT population were manually calculated for type, severity, and attribution, and are compared with comparisons of proportions z-test.
Post-hoc sensitivity analysis was performed for the patients in the PP population who reported outcomes early. Post-hoc subgroup analysis was performed for the patients in the PP population who reported symptoms other than pain alone to be their predominant symptom.
Plasma concentration was graphically illustrated in relation to overall improvement by CGI and number of adverse events for the patients in the PP population who received imipramine and delivered blood samples at the right time.
The analysis was done with Stata (version 13.1). The study is registered with ClinicalTrials.gov, number NCT01518634; The Ethics Committee of the Central Denmark Region, number 20110210; The Danish Health Authority, number 2011100742; The Danish Data Protection Agency, number 2007-58-0010 and EudraCT, number 2011-004294-87.

Role of the funding source

The funder of this study as well as the provider of the study drugs had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (JA) and the last author (PF) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. From January 30, 2012 to November 24, 2014, a total of 551 consecutively referred patients were screened for inclusion. 418 patients fulfilled diagnostic criteria for multi-organ BDS. Primary reasons for exclusion hereafter were psychiatric disorders demanding treatment or ongoing pain medication. The study was completed on May 1, 2015.
Discontinuation of antidepressants or pain-modulating drugs, besides paracetamol, was required for 51 patients (36·7%). A total of 139 patients were included and randomised after giving informed written consent. One written consent was given on an incorrect consent form, and this patient could not be reached to renew consent. All data regarding this patient were withdrawn.
125 (90·0%) received at least one dose of the study drug and were included in the ITT population. 65 patients (52·0%) were allocated to imipramine and 60 (48·0%) to placebo. Patient characteristics are given in Table 1. The mean number of FSS in both groups was 3·8. Pain was the predominate

symptom for a total of 28 patients (22·4%). The mean score of the SF-36 PCS was more than two standard deviations below population norms, indicating severe impairment. The placebo group tended to represent a group of lower socioeconomic status. Conversely, the placebo group had a lower level of psychiatric comorbidity and shorter illness duration.

Treatment was terminated prematurely for eight patients (12·3%) in the imipramine group and for seven (11·7%) in the placebo group. Seven dropped out because of adverse events: four patients (6·2%) from the imipramine group and three (5·0%) allocated to placebo. Rates and reasons for dropout did not differ between the groups.

A total of 110 patients (88·0% of the ITT population) underwent full treatment according to protocol (PP). 85 patients (77·3%) were titrated up to 75 mg imipramine or placebo. The remaining 25 patients (23·7%) attempted to increase dosages, but remained at 25 or 50 mg mainly due to adverse events. There were no differences in final dose received in the two groups.

The PP analysis data was complete with no missing values (n=110). In the ITT population (n=125), data were insufficient or missing for a total of five patients; for three patients, who dropped out of the study, outcome data were missing as the patients did not respond and could not be reached within adequate time. For two patients, outcome data were dealt with as missing data since outcomes were obtained either before treatment commencement or months after end of treatment. Sufficient data were obtained for 120 patients (96·0%). Outcomes were reported according to protocol for 101 (84·2%) of these patients, i.e. after 9-11 weeks of minimum 25 mg study drug, and for the remaining 19 patients (15·8%), outcomes were reported early (6·7-9 weeks) due to technicalities.

The randomisation code was not broken during the trial.

The raw data for the primary outcome are displayed in Table 2. Of the 120 patients who provided primary outcome data, 33 (53·2%) of those receiving imipramine responded “better” or “much better”, whereas this was the case for 14 patients (24·6%) receiving placebo. The analysis of the CGI score yielded an OR for an improved outcome with imipramine of 3·3 (95% CI 1·6-6·8); $p<0·001$ when using a proportional odds model. Using a worst-case scenario for the five patients with missing data in the ITT analysis, imipramine remained statistically significantly superior to placebo with an OR of 2·4 (95% CI 1·2-4·8); $p= 0·01$. The estimated number needed to treat for one additional patient to report improvement (better or much better) after imipramine compared with placebo was 3·6 (95% CI 2·3-8·9). The PP analysis of the CGI score yielded an OR for an improved

outcome with imipramine of 3·8 (95% CI 1·8-8·1); p<0·001.
The secondary outcomes for the PP population are shown in Figure 2. For the ITT population, the estimated group differences between imipramine and placebo were statistically and clinically significant on the SF-36 PCS (3·9 (95% CI 0·6-7·2)); p=0·022), SCL scale for somatisation (7·2 (95% CI 13·7-0·8)); p=0·028), the WHODAS 2.0 disability score (-7·8 (95% CI -15·0- -0·6)); p= 0·033 and illness worry measured by Whiteley-7 (10·4 (95% CI -17·1- 3·7)); p=0·003). No statistically significant differences between groups could be shown in neither ITT nor PP analysis for overall mental health (SF-36 MCS), social functioning (SF-36 SF), intensity of predominant symptom (NRS-11), functional somatic symptoms score (the BDS checklist) or symptoms of anxiety or depression (SCL scales).

For the patients in the PP population who reported other symptoms than pain to be predominant or who were equally bothered by both pain and other symptoms (n=84 (76·4%)), subgroup analysis of the primary outcome showed that the point estimate decreased slightly to an OR of 3·4 (95% CI 1·4-8·1); p=0·005.
The result of the primary outcome for patients who provided data on time in the PP population (n= 95 (86·4%) led to an OR of 4·1 (95% CI 1·8- 9·21); p<0·001.
We found no differences between groups for any changes in measurement from baseline to the intermediate measure at three weeks (before the wash-out period). In both groups, the depression scores from the SCL-92 were statistically significantly reduced from baseline to intermediate measure; for the imipramine group a reduction of an estimated -7·4 (-10·7--4·2); p<0·001 and in the placebo group an estimated -7·7 (-11·6--3·8); p<0·001. No within-group differences were found for the other intermediate outcomes (SCL-somatisation, SCL-anxiety), while a slight reduction in the BDS Checklist reached statistical significance in the placebo group by an estimated -3·0 (-6·0-0·04); p=0·047.

Adverse events attributed to imipramine treatment are shown in Table 3. 36 (55·4%) in the imipramine group experienced at least one adverse event of at least moderate intensity, whereas this was the case for 12 (20·0%) in the placebo group (p<0·000). The adverse events causing dropout in the placebo group were bruises, headaches, sweating, and increased blood pressure and pulse, and for the imipramine group the adverse events causing drop out were sedation, headaches, sweating

and dryness of the mouth. One patient had a serious adverse event during the trial; a subdural haematoma sustained after an accident. Study drug was discontinued.
Compliance was monitored regularly by the patients' report and by means of plasma concentration measures of imipramine and despiramine at end point. Four of the 110 patients who finished per protocol failed to deliver blood samples at the right time. One patient given imipramine presented with a plasma concentration under the detection limit. The remaining patients given imipramine presented with a plasma concentration of imipramine and despiramine ranging from 30 to 879 nmol/l. Figure 3 shows the plasma concentration in relation to overall improvement by CGI and number of adverse events.

Discussion

This single-centre, randomised, double-blind trial investigated the effect of low-dose imipramine in patients with multiple FSS defined by the criteria for the research diagnosis multi-organ BDS. This study demonstrates that a minimum dose of imipramine taken for 10 weeks supported by regular contacts to clinicians results in an improvement in patient-rated overall health and a series of other parameters including physical health, somatic symptom burden, and illness worry. Low-dose imipramine was not superior to placebo in improving mental health and social functioning. Adverse events were more common in the imipramine group, but only rarely led to discontinuation of treatment.

Our results are in line with those of other studies of low-dose imipramine/desipramine in patients with single FSS, though these studies are few and the results heterogeneous as regards outcome measures and study population.[22–24] A comparison of our results with those of existing literature on TCAs in general for patients with FSS or somatoform disorders shows a less clear picture.[1,6,9,25] In FM and IBS, though, the benefit from TCAs, especially that of amitriptyline, is comparable with the effect achieved in the present study although amitriptyline is associated with a very high dropout rate due to adverse events.[7,8]

The health improvement after imipramine was not exclusively attributable to pain relief, as those patients who did not report pain as their predominant symptom also experienced an overall health improvement after imipramine. The health improvement seems not attributable to change in mental health either, as neither the mental health scales of the SF-36 nor symptoms of anxiety or

depression improved after imipramine compared with placebo. This lack of differences in mental health between patients receiving imipramine and placebo allows us to conclude that the health improvement after imipramine in this study is not caused by an indirect effect of change in mental health, e.g. a relief in an underlying, sub-clinical depression. However, symptoms of depression decreased in both groups after wash-out before initiation of the primary intervention (10 weeks of minimum 25 mg study drug). Noteworthy, this is after the discontinuation of other medication, including antidepressants. This change may be owing to the thorough assessment and psychoeducation given in this study, providing the patients with a better understanding of their condition and inducing hope for recovery in both groups. However, this change can not explain the different improvements between groups at endpoint.

The proportion of patients with adverse events was high compared with rates reported in studies of low-dose imipramine in other patient groups.[26] Possible adverse events are not easily distinguished from fluctuations in symptoms of BDS, both for the clinician and for the patient. This may contribute to an overestimation of adverse events in this patients group. Another explanation could be that patients with multi-organ BDS are more susceptible to experiencing somatic symptoms, including adverse events. This is in line with some of the suggested possible pathophysiological mechanisms in BDS such as increased body awareness, symptom amplification, or central sensitisation.[27,28]

On the other hand, along with a possibly increased susceptibility, the patients seem to possess both robustness and stamina when experiencing negative symptoms. Despite the adverse events, treatment was continued by the large majority of the patients. The rate of dropout due to adverse events was remarkably low, especially when comparing with dropout rates in trials of amitriptyline in IBS and FM. A possible explanation is the difference in neurotransmitter affinity and the nature of the adverse events; patients with multiple FSS may better tolerate the adverse events of imipramine than those of amitriptyline. Other reasons for this increased tolerability and compliance could be the low start dose of 10 mg combined with the slow tapering of doses. Finally, the regular contact to the clinic and the psychoeducation delivered at treatment initiation could optimise patients' treatment expectations and their motivation to stay adherent in spite of negative symptom experiences.

The concentration-effect relationship of imipramine showed a considerable inter-individual variability. It is, however, noteworthy that in some patients with improvement after imipramine, we

found plasma drug levels as low as 100 nmol/L, and the majority of patients experiencing improvement presented with levels below 400 nmol/L. Also, our results point towards an association between increased plasma drug concentration and more adverse events. A larger study population with an initial analysis of fast and slow metabolisers is needed to further describe the concentration-response relationship.

Our trial has a number of strengths including a high compliance as well as a robust data collection with few missing outcomes. Other strengths are the double-blind, randomised design, the thorough assessment before inclusion, and the precise and reproducible diagnostic criteria of multi-organ BDS in this discipline of diagnostic confusion.[13] Furthermore, the treatment was delivered by several clinicians, enhancing the generalisability of our findings. Finally, imipramine is easily delivered, easily available, inexpensive, and produces treatment response at a relatively early stage.

Our trial, however, also has several limitations, one being the choice of outcomes. Both the primary and all secondary outcomes relied on patients' self-report with no additional clinician-rated or objective measurements of illness severity or functioning (e.g. walking distance, work ability). The effect of imipramine in these domains remains unclear. However, objective measurements are generally lacking in FSS research, which makes our study comparable to other similar trials.[29] Symptom scores are often proposed as the most reliable outcome measures in FSS. These measures have the inherent disadvantages of any symptom score system, i.e. they measure specific symptoms that might have no impact on the patients' global well-being. In studies of FM, symptom score improvement corresponds well with improvement measured by means of global scores.[20] Furthermore, global scores have the advantage of not being specific to certain FSS. We argue that patient-rated overall health improvement, our choice of primary outcome, reflect the most important end point in multi-organ BDS, especially considering the fluctuation in symptom location and severity and the wide and varied symptomatology of multi-organ BDS.
The higher rate of moderate adverse events in patients receiving imipramine could potentially have compromised successful blinding of treatment allocation. However, as only few patients in both groups did not experience any adverse events (10·8% in the imipramine group and 28·3% in the placebo group), and as we did not rely on clinician-rated outcomes, it seems unlikely that our findings are explainable by unsuccessful blinding.

The final dose of study drug for each patient was not guided by plasma concentration and we did not perform gene tests, which could have identified fast metabolisers of imipramine.[30] However, this may contribute to an underestimation rather than an overestimation of the effect of imipramine in some patients.

The generalisability of our study is affected by the fact that our study population represents the most severely affected and chronically impaired patients with multiple FSS referred to secondary care. It is unknown whether imipramine would be equally beneficial in other settings such as primary care, where patients may be less impaired and less chronically ill, or in psychiatric settings, where patients to a much higher degree may suffer from concomitant psychiatric disorders. Furthermore, physicians in other settings may be less experienced in managing FSS, and the thorough clinical assessment including the individualised psychoeducation provided in the present study is not easily delivered in all settings, especially not in primary care where time resources are limited. However, as we did include consecutive patients and the majority of the eligible patients participated in the trial, the study population is likely to be representative for the core group of severely affected patients with FSS without considerable medical or psychiatric comorbidity in secondary care. Nonetheless, with the moderate sample size in this study, results must be interpreted with caution and replicated in lager, preferably multi-centre, trials.

In conclusion, our study represents a step forward in the search for feasible treatment options for patients with multiple FSS who are often considered treatment-resistant. Ten weeks of low-dose imipramine supported by regular contacts to clinicians was an effective and tolerable treatment option that improved overall health, physical symptoms, and illness worry in patients with multiple FSS.

Contributors

JA, AS and PF designed the study. JA and JJ did the statistical analysis. JA wrote the first draft of the report. All authors were involved in the interpretation of the data. All authors critically reviewed, edited, and approved the final manuscript.

Declaration of interests

The Research Clinic for Functional Disorders, Aarhus University Hospital, Denmark received funding for this project from the Danish foundation, Trygfonden, and the study drugs were provided by Takeda Pharma A/S.

JA, AS, LG, JJ and PF declare no competing interests.

TJ reports personal fees from Pfizer, personal fees from Mundipharma, outside the submitted work.

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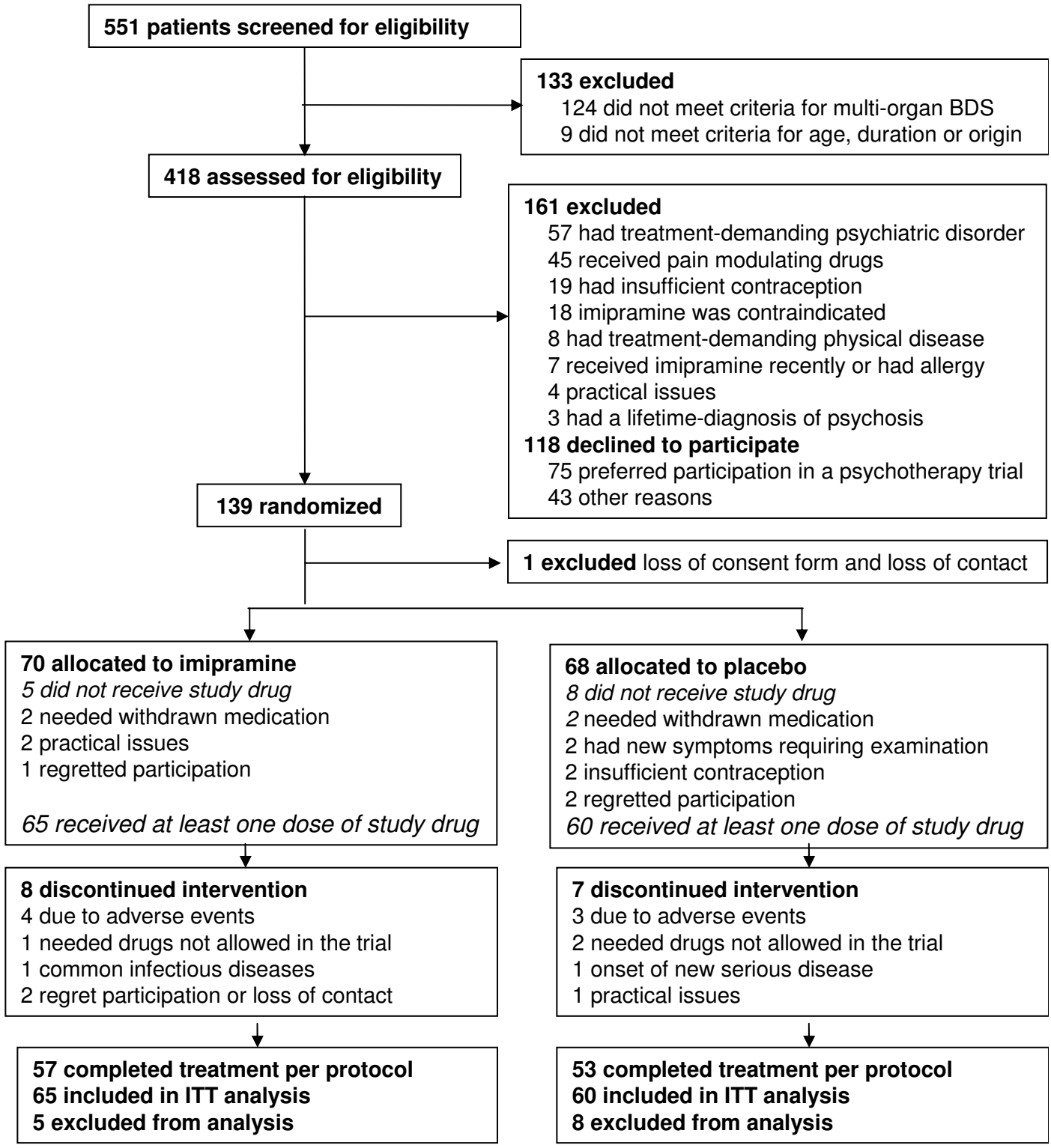

Figure 1. Trial profile

	Imipramine (n=65)	Placebo (n=60)
Age, years	36·6 (SD 8·6)	40·1 (SD 7·5)
Sex		
Male	12 (18·5%)	19 (31·7%)
Female	53 (81·5%)	41 (68·3%)
Married or living with a partner	48 (73·8%)	37 (61·7%)
Higher education[†]	21 (32·3%)	14 (23·3%)
Work status		
Employed or student	37 (56·9%)	24 (40·0%)
Of these on sick leave	13 (35·1%)	11 (45·8%)
Unemployed	18 (27·7%)	26 (43·3%)
Disability pension or flexible work	7 (10·8%)	10 (16·7%)
Illness duration, years*	9·0 (SD 7·7)	7·3 (SD 5·5)
Clinician-rated impairment in daily life*		
Moderate	15 (23·1%)	9 (15·3%)
Severe	50 (76·9%)	50 (84·8%)
Number of symptom clusters*	3·6 (SD 0·5)	3·8 (SD 0·4)
Musculoskeletal tension and pain syndrome	58 (89·2%)	49 (83·1%)
Gastrointestinal syndrome	30 (46·2%)	42 (71·2%)
Cardiopulmonary syndrome	23 (35·4%)	23 (39·0%)
General distress syndrome	51 (78·5%)	44 (75·6%)
Number of functional somatic symptoms*	34·4 (SD 8·2)	37·8 (SD 10·6)
Predominant symptom		
Pain	16 (24·6 %)	12 (20·0 %)
Other symptoms than pain	12 (18·5 %)	6 (10·0 %)
Pain and other symptoms equally dominate	37 (56·9 %)	42 (70·0 %)
Lifetime psychiatric comorbidity[§]		
Depression disorder	20 (30·8%)	16 (26·7%)
Anxiety disorder	13 (20·0 %)	12 (20 %)
Other[‡]	8 (12·3%)	3 (5 %)
At least one of the above	29 (44·6%)	23 (38·3%)
SF-36 Short Form Health Survey		
Physical component summary	31·7 (SD 7·9)	31·1 (SD 8·5)
Mental component summary	42·0 (SD 11·3)	39·8 (SD 11·9)
Physical functioning	59·7 (SD 21·8)	57·3 (SD 23·0)
Role-physical	20·4 (SD 28·6)	12·9 (SD 25·8)
Bodily pain	34·8 (SD 19·0)	30·2 (SD16·5)
General health	36·5 (SD 15·2)	36·9 (SD 16·7)
Vitality	24·6 (SD 19·8)	23·7 (SD 17·1)
Social functioning	49·4 (SD 25·6)	48·3 (SD 27·2)
Role-emotional	61·5 (SD 41·8)	52·2 (SD 42·7)
Mental health	60·4 (SD 17·7)	55·2 (SD 18·4)
Illness worry (Whitely-7)	40·2 (SD 25·9)	38·8 (SD 23·0)
SCL-92 Symptom Check List– 92		
Depression score	37·1 (SD 22·9)	42·6 (SD 23·1)
Anxiety score	29·7 (SD 21·5)	33·6 (SD 19·7)
Somatisation score	46·9 (SD 17·3)	48·8 (SD 16·6)
Functional somatic syndromes*[§]		
Chronic fatigue	52 (80·0%)	48 (81·4%)
Fibromyalgia	43 (66·2%)	44 (74·6%)
Irritable bowel syndrome	20 (30·8%)	23 (39·0%)
Non-cardiac chest pain	25 (38·5%)	35 (59·3%)
Tension headache	48 (73·9%)	40 (67·8%)
Number of functional somatic syndromes	3·8 (SD 2·5)	3·8 (SD 2·5)
Medication discontinued before inclusion[€]		
Tramadole, morfine, codeine	6 (9·2%)	10 (16·7%)
NSAIDs or triptans	10 (15·4%)	22 (36·7%)
Antidepressants	5 (7·7%)	8 (13·3%)
Antiepileptics	1 (1·5%)	3 (5·0%)
Other[$]	3 (4·6%)	3 (5·0%)

Data are n (%) or mean (SD)
*Based on functional somatic symptoms in the past 2 years, according to diagnostic interview and review of medical records. Data are missing for 1 of the 60 patients in the placebo group.
[†]At least medium-cycle higher education
[‡]Other psychiatric comorbidities, e.g. personality disorder, eating disorder, suicide attempt
[§]Allowing more than one diagnosis per patient.
[€]Allowing more than one drug per patient.
[$]Diuretics (3), cholesterole-reducing drugs (1), benxodiazepines (1), antipsychotics (1)

Table 1: Baseline characteristics of the ITT population

	Imipramine	Placebo
CGI-5 raw score		
Much worse	1 (1·5%)	1 (1·7%)
Worse	4 (6·2%)	11 (18·3%)
Unchanged	25 (38·5%)	31 (51·7%)
Better	22 (33·8%)	14 (23·3%)
Much better	11 (16·9%)	0 (0·0%)
Missing	2 (3·1%)	3 (5·0%)
Total	65 (100%)	60 (100%)

Data are in n (%) in response to the question: "How do you consider your health status now compared with when you first came to the clinic?"

Table 2. Primary outcome.

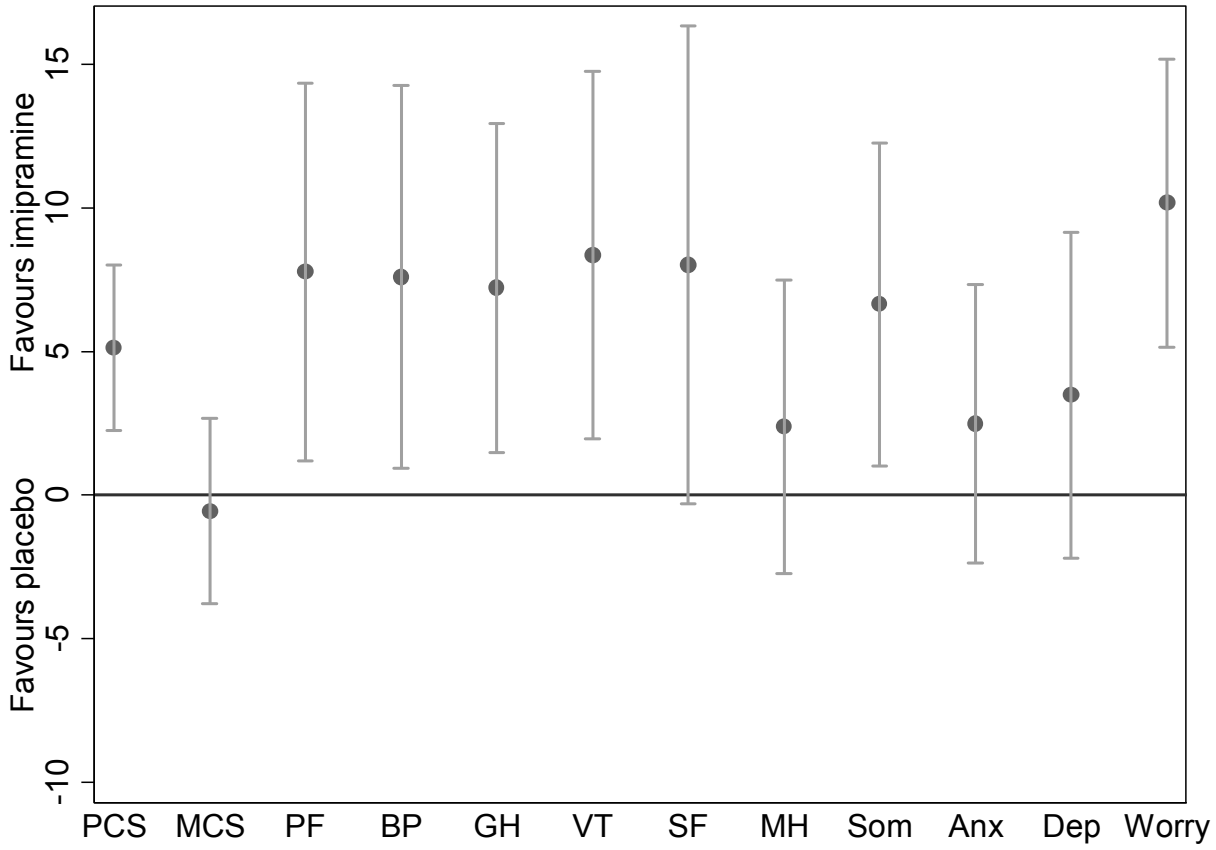

Figure 2. Secondary outcomes for patients finishing the study per protocol.
Estimates and 95%CI for the difference between groups after 10 weeks adjusted for baseline score for the PP population (n=110).
SF-36 subscales. PCS=Physical Component Summary, MCS=Mental Component Summary, PF=Physical Functioning, BP=Bodily Pain, GH=General Health, VT=Vitality, SF=Social Functioning, MH=Mental Health
SCL subscales. Som=Somatisation (symptom burden), Dep=Depression, Anx=Anxiety
Whiteley-7. Worry= Illness worry

	Imipramine (n=65)	Placebo (n=60)
Overall adverse events*		
No adverse events (AE)	7 (10·8%)	17 (28·3%)
At least one AE of at least moderate intensity^	36 (55·4%)	12 (20·0%)
Patient drop out due to AE	4 (6·2%)	3 (5·0%)
Specific adverse events *†		
Dry mouth	26 (40·0%)	8 (13·3%)
Dizziness	23 (35·4%)	7 (11·7%)
Nausea	14 (21·5%)	6 (10·0%)
Sweating	11 (16·9%)	4 (6·7%)
Sleep disturbances	10 (15·4%)	2 (3·3%)
Tiredness	10 (15·4%)	6 (10·0%)
Headache	8 (12·3%)	7 (11·7%)
Constipation	7 (10·8%)	2 (3·3%)
Other gastrointestinal symptoms	6 (9·2%)	4 (6·7%)
Change in weight or appetite	5 (7·7%)	2 (3·3%)
Mental change	5 (7·7%)	3 (5·0%)
Pain and tension	3 (4·6%)	3 (5·0%)
Restlessness	3 (4·6%)	1 (1·7%)
Urinary retention	3 (4·6%)	0 (0·0%)
Heart pounding	2 (3·1%)	2 (3·3%)
Vision disturbances	2 (3·1%)	2 (3·3%)
Paresthesia	2 (3·1%)	1 (1·7%)
Other‡	4 (6·2%)	7 (11·7%)

Data are in n (%)
* Adverse events possibly or definitely related to study drug
^ Scale for adverse events: light, moderate, severe
† Exact number of patients who experienced a specific adverse event of any intensity during the trial, i.e. dry mouth was reported by 26 patients (40%) during imipramine treatment
‡ Gathering of various adverse events occuring with a maximum frequency of two.

Table 3. Adverse events

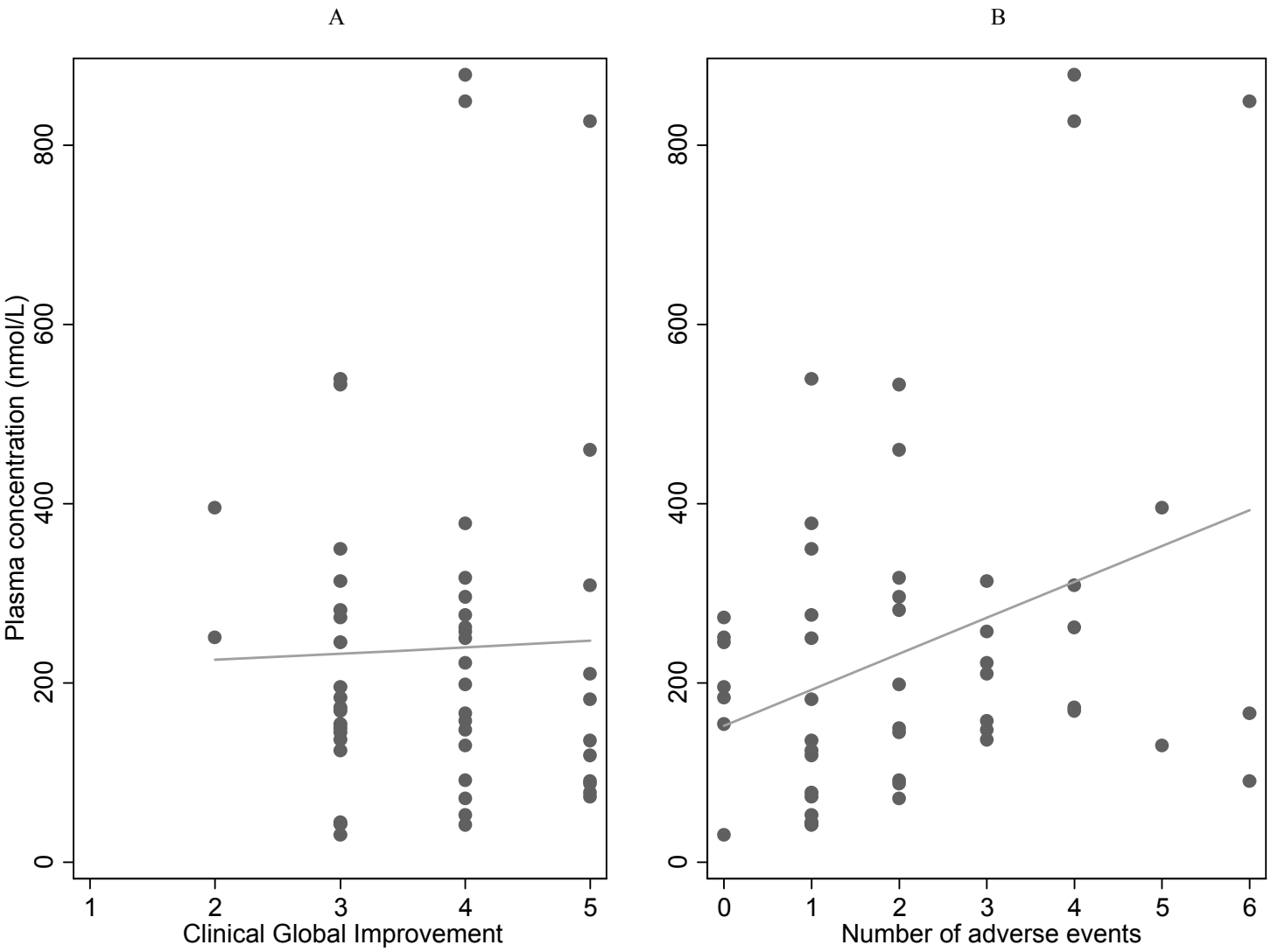

Figure 3. Plasma drug concentration and primary outcome (CGI) (A) and number of adverse events (B)
Plasma concentration of imipramine + desipramine.
(A) 1= much worse 2= worse 3= unchanged, 4= better 5= much better
(B) Number of adverse events regardless of intensity