

# An investigation of the long-term benefits of antidepressant medication in the recovery of patients with chronic fatigue syndrome

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Two hundred and seventy-five patients fulfilling the Centre for Disease Control (CDC) criteria for Chronic Fatigue Syndrome (CFS) completed measures assessing illness history, global ratings of well being, sleep, activity and psychopathology at baseline, 6 months, 18 months and 3 year follow-up. Forty-nine of these patients had been prescribed antidepressant medication, namely Tricyclic drugs or Selective Serotonin Re-uptake Inhibitors (SSRI). Data from the current study suggests that patients in the antidepressant medication group recover at a faster rate over time when compared to the untreated patient sample. In addition, the positive effects of antidepressant therapy are maintained at the 3-year follow-up point. It appears from these data that the SSRI in particular are responsible for improvements in the condition. Most importantly, these improvements include a reduction in the levels of fatigue recorded by patients. These findings have not been demonstrated in previous studies of the effect of antidepressant therapy for patients with this illness and this may reflect the short time periods studied in the earlier research. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS—Chronic Fatigue Syndrome; antidepressant medication; recovery

## INTRODUCTION

Fatiguing illnesses, in particular Chronic Fatigue Syndrome (CFS), are difficult conditions to accurately determine and quantify. Holmes *et al.* (1988) developed a working case definition for CFS, which provided a structured method for categorising the illness. Modified definitions such as the Oxford criteria, as described by Sharpe and colleagues (1991), and the Centre for Disease Control (CDC) criteria (Fukuda *et al.*, 1994) have added coherence and further guidelines for clinicians and researchers in the field. These criteria define a person suffering from CFS as one who has experienced persistent, debilitating fatigue for 6 months or more. Rest, in these patients, is not restorative and the fatigue state is not due to ongoing exertion. Onset is described here as 'definite' or 'new' and there may be several co-

existing symptoms present. The physical fatigue experienced in CFS produces a marked reduction in activity, and together with other ancillary symptoms such as pain and sleep disturbance, make the illness debilitating and persistent (Andersen *et al.*, 2004). The resulting illness leads to a substantial decrease in personal, social and occupational activities, severely affecting the patient's quality of life.

Both the cause of CFS and the mechanisms that maintain it remain largely unknown. Surawy *et al.* (1995) produced data suggesting that once the illness had established itself, cognitive, behavioural, emotional, physiological and social factors might work together to perpetuate it. Due to the complexity of the illness possible treatments have, therefore, been investigated on a pragmatic basis. Several centres have reported results from pharmacological based treatment studies which focused on agents that alleviate some of the symptoms associated with CFS (Goodnick *et al.*, 1992; Vercoulen *et al.*, 1996; Hickie *et al.*, 1999 for example). These include symptoms such as co-morbid anxiety and depression and problems of

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sleep disturbance which are often associated with CFS and other medically unexplained syndromes (O'Malley *et al.*, 1999). However, results from previous studies have been mixed, and although antidepressant therapy has been shown successful in terms of alleviating certain symptoms associated with the syndrome, there is no firm evidence to suggest that they facilitate recovery in CFS. In an in-depth review of treatments for CFS by Rimes and Chalder (2005), three randomised controlled trials (RCT) of two antidepressants; the Selective Serotonin Re-uptake Inhibitor (SSRI) fluoxetine (Vercoulen *et al.*, 1996) and the Monoamine-oxidase Inhibitor (MAOI) phenelzine (Natelson *et al.*, 1996), were discussed. Two of the RCTs reviewed, did not provide significant results for any of the outcome measures used in the trial; the third, again using fluoxetine (Wearden *et al.*, 1998) showed modest improvements in the level of depression expressed by patients in the antidepressant group but no positive effect on fatigue. There was no evidence to suggest that these agents provided any useful purpose in the treatment of CFS.

However, both therapy length and follow-up assessment point for the treatment trials described above were relatively short. For example, in the study conducted by Hickie (1999), nefazodone was administered to patients for a 6-week period followed immediately by the collection of the final assessment measures. Similarly, in the RCT described by Vercoulen *et al.* (1996), fluoxetine was administered to CFS sufferers for 8 weeks with a final data collection point 2 months post-therapy. It may be the case that both pharmacological intervention and final outcome data should be conducted over a longer time frame for any measurable improvement to become apparent. To illustrate this, studies conducted by Antelman and his colleagues (Antelman and Gershon, 1998 for example) suggested that the positive effects of antidepressant medication for major depressive illnesses continue and improve long after the cessation of treatment. In addition, this phenomenon, termed time-dependant sensitisation to antidepressant therapy, was indicated following even single treatments. It would, therefore, be of interest to follow CFS patients prescribed antidepressant medication over a longer time period.

Data collection for the current study formed part of an ongoing research programme investigating the characteristics and natural progression of CFS. Initial findings had already highlighted impairments associated with the illness such as mood and other psychopathological disturbance (Smith *et al.*, 1996). These problems became evident when comparing the

patient group with an age, gender and educationally matched healthy control group using a wide-ranging battery of questionnaires. Furthermore, these data were also collected at specific follow-up points in order to chart the typical illness history of these patients. Improvements in health-related measures taken at baseline could, therefore, be used to estimate recovery rates in the untreated patient over time. Once validated, these data provided a measure which could accurately evaluate patients' health status. In addition, the same measure was used to assess recovery from the condition and evidence from these studies suggested that spontaneous recovery from CFS is relatively rare at only 6% at 3-year follow-up.

When describing these data it was discovered that a small proportion of the patient sample recruited for the study had been prescribed antidepressant medication, either Tricyclic or SSRI antidepressants, at the time of referral. It was considered, therefore, that it would be of interest to investigate retrospectively the role antidepressant therapy plays in the recovery in the otherwise untreated patient. To achieve this, data from this sub-group of patients were compared to those patients not prescribed antidepressant medication in an attempt to provide evidence of the possible efficacy of these agents in recovery.

## METHODS AND MATERIALS

Ethical approval was granted by the appropriate local Health Authority. All participants gave informed consent and data was coded to protect the anonymity of the patients.

### *Design*

Data were collected longitudinally over a period of 3 years. The design was mixed, with the between-subject factor being antidepressant status and the within-subjects factor the various time points at which testing took place, that is, baseline, 6 months, 18 months and 3 years. Two sets of analyses were performed, one comparing health status (recovering or not recovering) in patients taking antidepressant medication with those taking no antidepressants, the other analysis compared, again, health status, but this time looking at differences between patients taking Tricyclic antidepressants, patients taking SSRI antidepressants and those taking no antidepressants.

### Participants

Patients attending a dedicated outpatient clinic fitting the CDC criteria for CFS (Fukuda *et al.*, 1994) were invited to join a research panel. Each patient completed a comprehensive range of questionnaires charting illness history and psychopathology. At the clinic, research registrars conducted a detailed examination of each patient's medical history, including previous and current antidepressant medication history.

### Questionnaires

A comprehensive range of measures was administered, including standardised demographic measures, a brief illness history questionnaire and a 28-item symptom check list (Smith *et al.*, 1996). The Beck Depression Inventory (Beck *et al.*, 1961) and the Spielberger Trait Anxiety Inventory (Spielberger *et al.*, 1971) were used to measure co-morbid depression and anxiety in this study and fatigue was also measured using the fatigue sub-scale of the Profile of Fatigue Related Symptoms (PFRS) questionnaire (Ray *et al.*, 1993). Recovery was calculated using the current state of health variable (Smith *et al.*, 1996). This self-rated five-item scale describes the current illness as: (a) worse than at any stage, (b) bad, (c) bad with some recovery, (d) recovering with occasional relapses and (e) almost completely recovered. Recovery was assessed by calculating changes in this measure over time. Sleep quality and activity levels were measured using individual five-item scales with responses ranging from 'much worse' to 'much better' (Smith *et al.*, 1996).

The questionnaires were completed at baseline, and then repeated again at 6 months and 3 years later. In addition, a shortened questionnaire, comprising the symptom check list and current state of health scale, was completed 18 months after the baseline measures.

### Data analysis

A series of Chi-squared analyses were conducted on categorical demographic variables and one-way analysis of variance (ANOVA) tests were conducted on continuous data at baseline. Analysis of variance and independent sample *t*-tests were conducted to highlight any differences between the groups over time.

### RESULTS

Data revealed that 17% of the cohort had been prescribed antidepressants at baseline. Approximately half of those taking antidepressants had been prescribed Tricyclics (53%) and the rest SSRI (47%). 61% of these individuals indicated that antidepressant therapy had been helpful in alleviating their symptoms. When considering illness onset type (gradual or acute), the acute onset sub-group was marginally less likely to be taking antidepressant medication than the gradual onset group ( $p = 0.07$ ). There were no associations between illness length and likelihood of taking antidepressant medication.

Firstly we considered antidepressant group as a whole. Table 1 describes the baseline demographic and illness history data for the antidepressant and no-antidepressant groups. These data reveal that there are no significant differences between the two groups at baseline.

Furthermore, data from the 28-item symptom check list provided little evidence of significant differences between the two groups at baseline (see Table 2). The one exception being that the antidepressant group were significantly more likely to rate depression as a symptom ( $p < 0.01$ ).

Independent sample *t*-test analyses provided no evidence to suggest that there were any differences between the two groups for any of the other measures recorded at baseline, including questionnaire measures of anxiety and depression.

At follow-up, however, several differences emerged. When recovery was considered (using the current state of health measure) the antidepressant group record greater recovery rates over time than the no-antidepressant group and these data reach significance at 3 years ( $p < 0.03$ ; see Table 3).

This profile of recovery is also indicated in terms of total symptom scores. In other words, there was a significant lowering of total symptom scores in the antidepressant group compared to the no-antidepressant group (see Table 4).

If we look at individual symptoms, significant differences were reported between the two groups at 18 month and 3 year follow-up as shown in Table 5.

These data suggests that patients taking antidepressant medication at baseline were significantly less likely to report symptoms, such as physical weakness, physical fatigue, aching joints and allergies at follow-up than the no-antidepressant group. There was also a marginal difference in the reporting of lack of concentration as a symptom in these patients at 3-year follow-up ( $p = 0.06$ ). The fatigue sub-scale of

Table 1. Demographic data for the antidepressant/no-antidepressant patient groups at baseline

Baseline measure	No-antidepressant (n = 226)	Antidepressant (n = 49)
Gender:		
Male	31%	20%
Female	69%	80%
Age	42 (0.80)	44 (1.37)
Marital status:		
Single	21%	19%
Married	66%	67%
Divorced/separated	10%	8%
Widowed	3%	6%
Employment status:		
Employed	28%	26%
Unemployed	40%	33%
On sick leave	13%	25%
Other (homemaker/retired)	19%	16%
Illness history and beliefs:		
Illness onset type:		
Acute	63%	50%
Gradual	37%	50%
Illness duration (months)	62.1 (3.84)	65.9 (7.41)
Total symptom scores (maximum = 28)	15.8 (0.36)	15.5 (0.84)
Viral cause (suggested by patient)	65%	58%
Specific event	84%	90%

Table 3. Current State of Health scores for the antidepressant/no-antidepressant groups at baseline, 6 month, 18 month and 3 year follow-up. Values are expressed as a percentage

Current state of health measure:	No antidepressant	Antidepressant
Baseline		
Worse than at any stage	8.0	12.2
Bad	19.9	16.3
Bad with some recovery	43.4	32.7
Recovering with relapses	27.9	38.8
Almost recovered	0.9	0.0
6 months		
Worse than at any stage	8.5	7.9
Bad	13.7	18.4
Bad with some recovery	39.9	23.7
Recovering with relapses	35.9	39.5
Almost recovered	2.0	10.5
18 months		
Worse than at any stage	8.5	5.3
Bad	20.5	18.4
Bad with some recovery	36.9	26.3
Recovering with relapses	27.8	34.2
Almost recovered	6.3	15.8
3 years		
Worse than at any stage	7.2	8.3
Bad	14.4	8.3
Bad with some recovery	33.0	29.2
Recovering with relapses	39.2	25.0
Almost recovered	6.2	29.2

the PFRS also indicates a significant difference in the level of fatigue expressed by the antidepressant group at 6 months (antidepressants = 53.97; no-antidepressants = 60.00;  $t = 1.97$ ,  $df = 184$ ,  $p < 0.05$ ) and 3 years (antidepressants = 49.71; no-antidepressants = 58.17;  $t = 2.03$ ,  $df = 118$ ,  $p < 0.04$ ), indicating that the antidepressant group were reporting

lower levels of fatigue than the no-antidepressant group.

In addition, patients in the antidepressant group were significantly more likely to report improvements in quality of sleep over the 6-month follow-up period (antidepressants = 24%; no-antidepressants = 5%;  $\chi^2 = 9.89$ ,  $df = 2$ ,  $p < 0.001$ ) and at 3-year follow-

Table 2. Individual Symptoms for the antidepressant/no-antidepressant groups at baseline expressed as the percentage reporting the symptom

Symptom	No antidepressant	Antidepressant	Symptom	No antidepressant	Antidepressant
Physical weakness	81.4	81.6	Sensitivity to noise	58.8	61.2
Physical fatigue	86.7	81.6	Sensitivity to light	52.7	44.9
Legs feeling heavy	80.1	75.5	Fever	77.4	79.6
Muscle pain	89.4	89.8	Sweating	54.4	61.2
Chest pain	43.8	34.7	Shivering	43.8	40.8
Aching joints	69.0	65.3	Swollen glands	45.1	38.8
Nausea	46.0	36.7	Racing heart	45.1	46.9
Indigestion	39.8	34.7	Insomnia	47.3	55.1
Stomach feeling bloated	53.1	53.1	Depression	36.7	55.1*
Wind	49.1	44.9	Feelings of panic	41.2	42.9
Sore throat	52.2	51.0	Loss of concentration	90.7	83.7
Headache	69.9	73.5	Loss of memory	75.7	75.5
Earache	32.7	20.4	Allergies	35.4	28.6
Sore eyes	54.9	61.2			

\* $\chi^2 = 5.67$ ,  $df = 1$ ,  $p < 0.014$ .

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Table 4. Total Symptom scores for the antidepressant /no-antidepressant groups at baseline, 6 month and 3 year follow-up. Scores are the group means with s.e.m in parenthesis (maximum score = 28)

Total Symptoms	No Antidepressant	Antidepressant	F, df, p
Baseline	15.84 (0.36)	15.47 (0.84)	n/s
6 months	14.90 (0.49)	13.60 (1.07)	n/s
18 months	14.67 (0.46)	12.24 (1.13)	4.671, 1,213, $p < 0.032$
3 years	15.12 (0.59)	11.75 (1.29)	6.281, 1,119, $p < 0.014$

up (antidepressants = 29%; no-antidepressants = 7%;  $\chi^2 = 9.89$ ,  $df = 2$ ,  $p < 0.007$ ). Furthermore, patients in the antidepressant group reported higher activity levels than the no-antidepressant group (antidepressants = 21%; no-antidepressants = 4%;  $\chi^2 = 9.89$ ,  $df = 2$ ,  $p < 0.02$ ).

To investigate these findings further, the group of patients taking antidepressant medication were split into those taking the Tricyclic and related group of antidepressants and those taking SSRI and again compared to the no-antidepressant group.

Again there were no significant differences between the demographic nature of three groups at baseline or in the type of illness onset (acute or gradual) and duration. Patients in the SSRI group were significantly more likely to be in employment at baseline than the Tricyclic or no-antidepressant groups (SSRI = 49%, Tricyclic = 15%, no-antidepressant = 28%;  $\chi^2 = 6.34$ ,  $df = 2$ ,  $p < 0.04$ ). However, data from the current state of health measure indicated no difference in illness severity between the three groups at baseline.

In terms of recovery, patients in the SSRI group were marginally more likely to be in the 'almost completely recovered' section of the health status

scale than the Tricyclic or no-antidepressant group at 6 months ( $p = 0.06$ ) and 18 months ( $p = 0.06$ ). These data did, however, reached significance at 3-year follow-up (SSRI = 43%, Tricyclic = 10%, no-antidepressant = 6%;  $\chi^2 = 22.07$ ,  $df = 8$ ,  $p < 0.005$ ). As reported in previous studies, there is an association between the current state of health variable with total symptom scores. Table 6 describes the mean total symptom scores at baseline, 6 and 18 months and 3 year follow-up points.

At baseline, patients in the Tricyclic antidepressant group reported significantly higher total symptom scores than the SSRI group. The total symptoms scores for both antidepressant groups were lowered at 18 months and 3-year follow-up compared to the no-antidepressant group but only the SSRI group reaches significance.

Again, there were differences in individual symptom reporting at 18 months and 3 years (Table 7).

It is clear from these data that it is specifically the SSRI group of patients who were responsible for the decreased reporting of symptoms such as physical weakness and fatigue and aching joints. The fatigue sub-scale of the PFRS questionnaire also confirms this by providing data to suggest that there is an improvement in fatigue scores in the SSRI group over time.

The quality of sleep measure indicated that there was a significant improvement at 3-year follow-up in the SSRI group (SSRI = 43%, Tricyclic = 10%, no-antidepressant = 7%;  $\chi^2 = 20.62$ ,  $df = 4$ ,  $p < 0.001$ ). Interestingly, this group also reported significantly increased activity levels at 3-year follow-up (SSRI = 29%, Tricyclic = 10%, no-antidepressant = 4%;  $\chi^2 = 11.50$ ,  $df = 4$ ,  $p < 0.02$ ).

There were no differences between any of the groups in terms of co-morbid anxiety and depression at baseline (Spielberger *et al.*, 1971; Beck *et al.*, 1961). In addition, there were no significant improvements in the psychopathology of these groups over the follow-up period. However, the significant difference between the groups when reporting depression as a major symptom (on the 28-item check list) at baseline is lost at subsequent follow-up points.

Table 5. Individual Symptom Scores for the antidepressant/no-antidepressant groups at 18 months and 3 year follow-up. Scores are expressed as the percentage of patients reporting the symptom

Symptom	No antidepressant	Antidepressant	$\chi^2$ , p (df = 1)
18 months:			
Physical fatigue	77	55	7.272, <0.008
Chest pain	36	21	3.282, <0.049
Aching joints	73	55	4.507, <0.029
Noise	63	45	4.369, <0.029
Light	56	32	7.268, <0.006
Shivering	36	18	4.286, <0.027
Allergies	32	8	9.291, <0.001
3 years:			
Physical weakness	79	50	8.538, <0.005
Physical fatigue	75	50	5.873, <0.017
Aching joints	76	54	4.660, <0.031
Fever	73	50	4.805, <0.028
Allergies	32	8	5.414, <0.014

Table 6. The total symptom scores for the SSRI, Tricyclic and no-antidepressant groups at baseline, 6 months, 18 months and 3 year follow-up. Scores are the group means with s.e.m in parenthesis (maximum score = 28)

Total symptoms	No antidepressant	SSRI ( <i>n</i> = 23)	Tricyclic ( <i>n</i> = 26)	F, df, <i>p</i>
Baseline	15.84 (0.36)	13.43 (0.89)	17.27 (1.28)	3.063, 2, 272, <i>p</i> < 0.048
6 months	14.90 (0.49)	13.09 (1.42)	14.23 (1.64)	<i>n/s</i>
18 months	14.67 (0.46)	10.32 (1.38)	14.16 (1.72)	4.155, 2, 211, <i>p</i> < 0.017
3 years	15.12 (0.59)	10.93 (1.70)	12.90 (2.03)	3.455, 2, 118, <i>p</i> < 0.035

## DISCUSSION

Data collection for the current study was conducted as part of a larger project aimed at charting the natural progression of CFS over time in a cohort of untreated patients. On referral to a specialised out-patient clinic, each patient completed a lengthy medical examination with medical staff who also recorded a detailed account of each patient's illness history. When data collection was completed, descriptive analyses revealed that a small sub-group of patients (*n* = 49) had been prescribed antidepressant medication at the time of referral. The antidepressant therapy sub-group was comprised of patients who had been prescribed one of two antidepressant groups, namely the Tricyclic or SSRI antidepressants. An important feature of this study was to investigate the effect these agents had on CFS and whether antidepressant therapy does indeed assist recovery. To achieve this, data from the antidepressant medication sub-group were compared to that of the CFS sample as a whole (*n* = 226).

The baseline data indicated that there were no significant differences in the demographic nature of those patients taking antidepressant medication and those who were not. This was also true for the number of symptoms reported and health status of the two groups at baseline. This means that any differences seen at subsequent follow-up points can not be

attributed to confounding variables such as age and gender differences or illness severity.

Data collected at follow-up suggests recovery rates of 10.5% in the antidepressant group at 6 months compared to only 2% in the non-antidepressant group. Furthermore, this recovery rate continued to improve over time reaching 29.2% by the 3-year follow-up point (compared to only 6% in the non-antidepressant group).

Previous studies had indicated that changes in the current state of health measure (used to assess recovery) were linked to changes in other health-related measures. For example, improvements in the health status measure were accompanied by a lowering in the total number of symptoms recorded. Data from the current study confirmed this association; the antidepressant group also reported fewer symptoms than the non-antidepressant group at follow-up. When considering the symptom checklist in terms of individual scores, the antidepressant group reported lower levels of physical weakness and fatigue and fewer cases of aching joints. Furthermore, a decrease in reporting depression as a major symptom was also observed in the antidepressant group over time. In addition this group also reported improvements in activity levels and quality of sleep over the follow-up period. Previous studies had indicated that psychomotor, memory and attention deficits reported in CFS

Table 7. Individual Symptom Scores for the SSRI, Tricyclic and no- antidepressant groups at 18 months and 3 year follow-up. Scores are expressed as the percentage of patients reporting the symptom

Symptom	No antidepressant	SSRI	Tricyclic	$\chi^2$ , <i>p</i> (df = 1)
18 months:				
Physical weakness	77	42	89	13.652, <i>p</i> < 0.001
Physical fatigue	77	37	74	13.799, <i>p</i> < 0.001
Aching joints	73	42	68	7.618, <i>p</i> < 0.022
Light	56	21	42	8.954, <i>p</i> < 0.011
Allergies	32	5	10	9.422, <i>p</i> < 0.009
3 years:				
Physical weakness	79	29	80	16.470, <i>p</i> < 0.001
Physical fatigue	75	36	70	9.154, <i>p</i> < 0.010
Aching joints	76	43	70	6.788, <i>p</i> < 0.034

appeared to reflect those seen in sleep disorders and physical de-conditioning (Smith *et al.*, 1996). It could be that by addressing sleep quality, antidepressant therapy is facilitating recovery in this patient group.

The antidepressant group was further sub-divided into those taking Tricyclic antidepressants or SSRIs and compared again to the no-antidepressant group. Again, there were no differences between the three groups in terms of demographics or illness severity at baseline. Comparisons provided some interesting data; in particular, those results indicating improvements over time. These seem more favourable when focussing on the SSRI antidepressant group. Forty-three per cent of this group reported their state of health as 'almost completely recovered' at the 3-year follow-up point. This was a considerable improvement when compared to the un-treated sample recovery rate of 6%. In addition, the SSRI group recorded significant improvements in total symptom scores over time. Most importantly, these improvements were seen in symptoms such as physical weakness and fatigue which are two of the most common symptoms reported by sufferers in previous studies. In addition, patients with CFS typically report problems with sleep quality and maintaining levels of physical activity; the SSRI antidepressant data indicated improvement in both areas.

One important drawback to the current study is its retrospective nature, we do not, therefore, possess information relating to the length of intervention, the dosage of medication or the specific drugs used. Similarly, we are unable to address the extent to which patients in the antidepressant group were a self-selecting subgroup of CFS. Anecdotal evidence suggests that patients with this illness are reluctant to take antidepressant medication and many report 'sensitivity' to them. However, even when one takes these factors into consideration, there was evidence to suggest that antidepressant medication, particularly the SSRIs, do, in fact, facilitate recovery in CFS. Furthermore, these improvements included a measurable reduction in level of fatigue suffered by patients, an outcome which has not been demonstrated previously.

Although the long-term practical benefits of antidepressant medication for patients with CFS are indicated by these findings further research into these positive effects is required. Two studies are indicated: (a) a comparison of patients prescribed long-term medication with those taking antidepressants for only short periods and (b) short-term antidepressant use followed by the long-term monitoring of their effects, which would replicate studies conducted by Antelman and Gershon (1998). In addition, patients would be

randomly assigned antidepressant or placebo. In this way it may be possible to maximise the benefits of this type of medication for facilitating recovery in CFS using minimal intervention periods.

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