



ORIGINAL ARTICLE

SSRI Induced Apathy Syndrome

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ABSTRACT

Objective: Apathy is defined as diminished motivation and reduced goal-directed behavior accompanied by decreased emotional responsiveness. Besides being a symptom of some neurological conditions and psychiatric disorders, apathy is also known to be an adverse effect of antidepressants. Although attention to antidepressant-induced apathy has been increasing in recent years, studies about apathy are still very limited and generally presented as case reports. Despite being an important cognitive side effect of antidepressants it is not well recognized and may be misinterpreted as a residual symptom of the psychiatric disorder by clinicians. In this study, we aimed to analyze apathy levels of patients with anxiety disorders (AD) and major depressive disorder (MDD) before and after antidepressant treatment, with a prospective design.

Methods: Our study included 20 MDD and 20 AD patients admitted to Mersin University Research and Training Hospital, Outpatient Clinic of Psychiatry, who have not taken any antidepressant medication for at least last one month. Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A) and Apathy Evaluation Scale (AES) were administered before antidepressant treatment and on the 6th week of the treatment. Correlations and relationships between scale scores were analyzed.

Results: Thirty-five (87,5%) of the 40 patients were taking Selective Serotonin Reuptake inhibitors (SSRIs), while 5 (12,5%) were taking Serotonin-Noradrenalin Reuptake Inhibitors (SNRIs). In the whole group of patients, AES scores increased from a mean of 20,5 at baseline to 25 after antidepressant treatment ($p<0,05$). The increase in AES scores were significant only in patients taking SSRIs ($p<0.001$). Symptoms of depression and anxiety were improved in both patient groups. The mean HAM-D scores before and after treatment were 17,8 and 8,2 in MDD patients, respectively ($p<0,05$). The mean HAM-A score was 18,6 in AD patients before treatment, which decreased to a mean of 9,9 points after treatment ($p<0,05$).

Conclusion: Despite the reduction in depression and anxiety scores, six weeks of treatment with SSRIs was associated with the development of apathy in our study group, consisting of patients with MDD or AD. Clinicians should bear in mind that apathy is likely to occur within weeks of SSRI treatment and screen for it during the course of treatment.

Keywords: Anxiety disorder, apathy, major depressive disorder, SSRI, SNRI, side effect

INTRODUCTION

Apathy is defined as separate psychiatric syndrome with three dimensions: emotional, cognitive, and behavioral (motor). The behavioral symptoms are decreased productivity and lack of initiative, while the cognitive symptoms are noted as lack of interest, demotivation

about making plans for the future, and the emotional symptoms as blunted affect and negligence (1). Apathy can cause significant impairments in quality of life and productivity of person as well as disturbance of social, emotional, and physical well-being.

Selective serotonin reuptake inhibitors (SSRIs) are widely used in the treatment of major depression. They have reasonable efficacy with better safety and tolerability profile compared to older agents. However, SSRIs are not devoid of adverse effects. Some patients report that they experience a restricted emotional range and cannot get a normal emotional responsiveness to everyday events. It is sometimes described as a behavioral

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and affective indifference. Although most clinicians probably encountered patients on SSRI medication who reported the experience of apathy or emotional blunting, this clinical phenomenon has not undergone substantial research to date. It is not clear whether these experiences represent residual symptoms of depression or relate to mode of action of the SSRIs. In the last two decades, there have been case reports about occurrence of apathy or loss of motivation during treatment with SSRIs in children and adults (2). Apathy presenting in the absence of depression is related to long-term SSRI treatment and defined as SSRI-induced apathy syndrome which is a late-onset, dose-dependent, and reversible clinical condition. This syndrome is generally ignored or misinterpreted as a symptom of underlying depression psychopathology or treatment failure. The latter may lead to an unnecessary increase in antidepressant dose, resulting in impairment of social and occupational functioning because of worsening apathy.

Despite the increased rate of antidepressant use, studies on apathy as an adverse effect of antidepressants are very limited. Data about SSRI-induced apathy mostly consist of case reports or retrospective studies. Therefore, we aimed to prospectively determine the occurrence of apathy during antidepressant treatment.

METHODS

Study Sample

Patients presented to Mersin University Research and Practice Hospital, Outpatient Clinic of Psychiatry and diagnosed with Major Depressive Disorder (MDD) or Anxiety Disorders (AD) were included in the study. A total of 40 patients between 18-65 years of age, without any medical illnesses and free of any psychotropic drugs at least for the last month were included. Patients with comorbid psychiatric disorders (i.e., comorbid depression in anxiety group) were excluded. We used the Structured Clinical Interview for DSM-IV (SCID-I) for diagnosis.

All study procedures were approved by the Institutional Review Board at the of Mersin University.

Psychometric Scales

Sociodemographic Data Form: A semi-structured questionnaire consisting of demographic (age, gender, marital status etc.) and clinical (disease duration, past psychiatric history presence of medical conditions etc.) questions were given to all participants.

Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I): This form is a structured interview for making the major DSM-IV Axis I diagnoses which is administered by mental-health professionals. It's developed by Spitzer et al and reliability and validity studies of Turkish version were made by Özkürkçügil et al. (3,4).

Hamilton Depression Rating Scale (HAM-D): HAM-D is the most widely used clinician-administered depression assessment scale and used to determine a patient's level of depression before, during and after treatment. It contains 17 questions in Turkish version. A score of 0-7 is considered to be normal, 8-15 points mild, 16-28 moderate and above 29 indicates severe depression. HAM-D scale is developed by Hamilton and improved by Williams, and the Turkish validity and reliability study was performed by Akdemir et al. (5,7).

Hamilton Anxiety Rating Scale (HAM-A): HAM-A is a multiple item questionnaire used to assess the severity of symptoms of anxiety. It includes 13-item in Turkish version, administered by a health care provider. 14-17 points indicate mild anxiety, 18-24 moderate and above 25 indicate severe anxiety. Scale is mainly focused on the physical symptoms of anxiety (8). Turkish validity and reliability study was made by Yazici et al. (9).

Apathy Evaluation Scale (AES): AES is developed to distinguish apathetic patients from non-aphathetic patients and depressed patients (10). The scale consists of 18 items questioning last 1 month. It is applied by a mental health professional. The total score varies between 18-72. High scores represent more severe

apathy. Turkish validity and reliability were studied by Gülseren et al. (11).

HAM-D, HAM-A and AES were administered to patients before SSRI/ SNRI treatment started and after 6 weeks of treatment.

Statistical Analysis

The Shapiro-Wilk test was used to test for normality distribution in all continuous variables. The relationship between the three different scales was tested with Spearman's correlation coefficient. Student t test for normal distributions and Mann-Whitney U tests for non-normal distribution were performed. Paired sample t test or Wilcoxon's sign rank tests were used for the differences between the measured values at two different time points. Descriptive statistics were presented as mean and standard deviation for normal distributions and minimum, maximum, median, 25-75% percentiles for non-normal distribution. $p < 0.05$ value was considered as statistically significant.

RESULTS

Forty patients were included in the study, 20 with MDD and 20 with AD (4 patients with generalized anxiety disorder, 3 social phobia, 2 obsessive compulsive disorder, 7 anxiety disorder NOS, and 4 panic disorder). SSRIs and SNRI were started at fixed doses (fluoxetine 20 mg, sertraline 50 mg, escitalopram 10 mg, paroxetine 20 mg, and venlafaxine 75 mg per day) and no dose change was made until the end of 6th week. The average age of the study sample was 37 (± 13.7) in MDD and 38 (± 11.4) in AD group.

Patients on antidepressant treatment were divided into SSRI and SNRI groups. The treatment arms did not show a uniform distribution; sertraline was used in 25% of total sample, whereas fluoxetine 15%, paroxetine 15%, escitalopram 32.5% and venlafaxine were given to 12.5% of the patients. Choice of medication was made on an individual basis considering past treatments, primary symptoms and potential side effects.

Depression and anxiety symptoms decreased

Table 1: Changes in the HAM-D and HAM-A scores of the MDD and AD groups

	HAM-D		HAM-A	
	Baseline	6 th week	Baseline	6 th week
MDD	17.85 \pm 5.71	8.2 \pm 8.25	23.85 \pm 8.29	13.70 \pm 6.25
AD	9.6 \pm 5.71	3.9 \pm 4.71	18.65 \pm 8.27	9.90 \pm 5.97

significantly in both patient groups after treatment (Table 1). The change in AES scores before and after treatment in the MDD and the AD group were found to be significant ($p < 0.001$) (Figure 1).

The mean baseline scores of HAM-D and HAM-A had a significant correlation with the mean baseline and endpoint AES scores. The mean endpoint HAM-A score did not have a correlation with endpoint AES score while endpoint HAM-D score had a significant correlation with endpoint AES scores (Table 2).

AES scores increased in all antidepressant groups by the end of 6th week. However, differences in AES scores pre-and post-treatment were significant for all SSRIs but not SNRI (Table 3). AES item-by-item analysis showed statistical differences in questions 1,6,7,8,9,10,11,13,14,15, and 16 (Table 4).

DISCUSSION

We found that while symptoms of depression and anxiety responded to treatment, six weeks of treatment with SSRIs but not SNRI was associated with the development of apathy in our study group. It has been known that SSRIs may cause cognitive side effects such as impairment of memory, concentration, and attention as well as apathy (12,14). Patients with MDD who present cognitive symptoms following antidepressant treatment have worse functional outcomes, are less likely to remit and tend to have more relapses (14). Evaluation of cognitive side effects of SSRIs is a challenging task because of overlap between side effects and residual symptoms of depression. Symptoms such as fatigue, cognitive impairment, apathy, irritability, and sleep and appetite changes may represent features of depression as well as antidepressant side effects (15). Thus, we separated study population in two groups as MDD and AD to assess

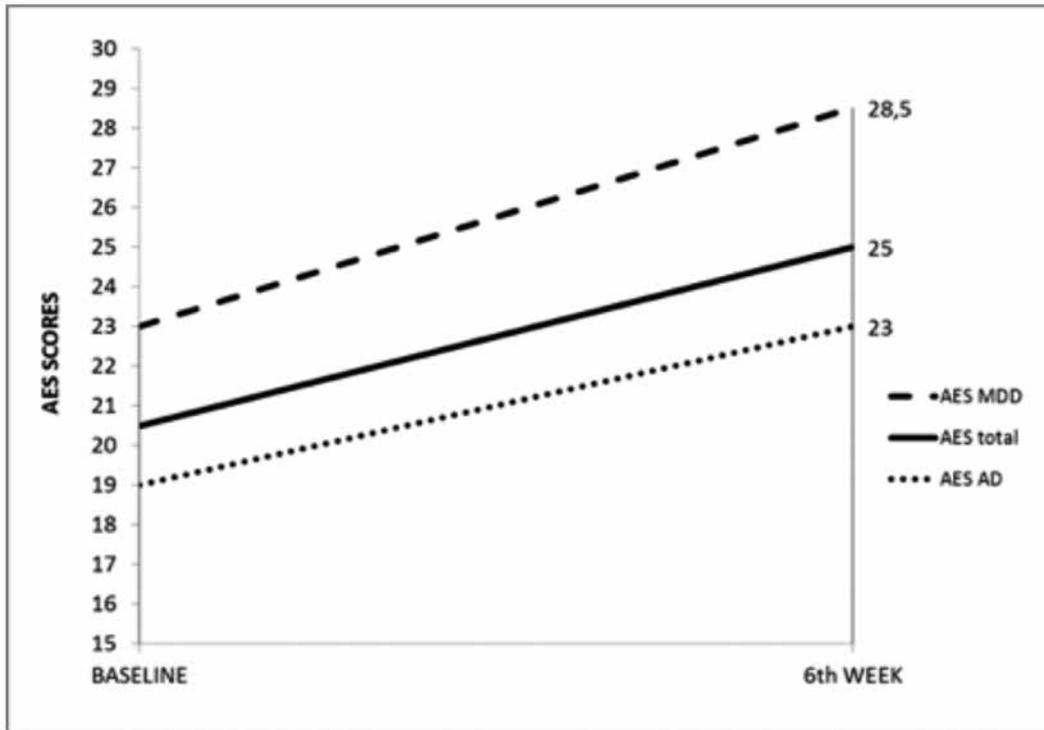


Figure 1: Changes of AES scores in the patient group

Table 2: Correlations between the scales

		HAM-A1	HAM-D2	HAM-A2	AES-1	AES-2
HAM-D1	r	0.635	0.709	0.510	0.748	0.575
	p	<0.001	<0.001	0.001	<0.001	<0.001
HAM-A1	r		0.618	0.854	0.432	0.371
	p		<0.001	<0.001	0.005	0.018
HAM-D2	r			0.734	0.441	0.433
	p			<0.001	0.004	0.005
HAM-A2	r				0.314	0.297
	p				0.048	0.063
AES-1	r					0.632
	p					<0.001

HAM-D₁: baseline, HAM-D₂: endpoint, AES-1: baseline, AES-2: endpoint

whether apathy is a side effect of antidepressants or a residual symptom. We found that both groups showed a significant increase with respect to AES scores after 6 weeks of treatment with SSRIs. The finding that endpoint AES scores of patients with AD also increased compared to baseline, suggests that apathy is an adverse effect rather than being a residual depressive symptom.

Several case reports of SSRI-induced apathy have been published, involving all SSRIs and various diagnoses

in adults, children and adolescents. However, large-scale epidemiological studies of SSRI-induced apathy are lacking. In a study of 161 SSRI treated patients, Bolling and Kohlenberg found that 20% of patients reported apathy (12). Fava et al. studied patients with MDD taking antidepressant treatment for at least 3 months and found that of the 117 patients meeting response criteria for depression, more than 30% on any antidepressant reported apathy (16).

Table 3: AES scores in antidepressant groups

Antidepressants (n)	Min-max	Median %25–75 percentage	Min-max	Median %25–75 percentage	P
Sertraline (n=10)	18–23	19 (18–22.25)	18–32	23.5 (19–28.5)	0.011
Escitalopram (n=13)	18–32	21 (18.5–24.5)	20–35	24 (23–31)	0.018
Fluoxetine (n=6)	18–29	22 (19.5–26)	25–32	28 (25–30.5)	0.027
Paroxetine (n=6)	19–22	20 (19–21.25)	21–28	24.5 (23.25–25.75)	0.027
SNRI (n=5)	19–23	20 (19.5–22.5)	21–29	23 (21.5–27)	0.176

Table 4: AES item-by-item analysis

Item	Baseline AES		Endpoint AES		P
	Min-max	Median 25–75% percentage	Min-max	Median 25–75% percentage	
1 (interested in things)	1–2	1 (1–1)	1–3	3 (2–3)	<0.001
2 (gets things done during the day)	1–2	1 (1–2)	1–3	1 (1–2)	1.000
3 (getting things started on by own is important)	1–2	1 (1–1)	1–2	1 (1–1)	0.564
4 (interested in having new experiences)	1–2	1 (1–1)	1–2	1 (1–1)	0.739
5 (interested in learning new things)	1–2	1 (1–1)	1–2	1 (1–1)	1.000
6 (puts a little effort into anything)	1–2	1 (1–2)	1–3	2 (1–2)	<0.001
7 (intensity in life)	1–2	1 (1–1)	1–2	1 (1–1)	0.002
8 (ending a job)	1–3	1 (1–1)	1–3	1 (1–2)	0.003
9 (spends time doing things that interest)	1–2	1,5 (1–2)	1–3	1 (1–2)	0.034
10 (have to be told what to do)	1–1	1 (1–1)	1–2	1 (1–1)	0.046
11 (negligence to problems)	1–2	1 (1–1)	1–3	2 (1–3)	<0.001
12 (has friends)	1–2	1 (1–1)	1–1	1 (1–1)	0.317
13 (give importance on getting together with friends)	1–2	1 (1–1)	1–3	1 (1–2)	0.012
14 (excitement when good things happens)	1–2	1 (1–1)	1–3	1 (1–2)	0.001
15 (accuracy of understanding problems)	1–2	1 (1–2)	1–3	1 (1–2)	<0.001
16 (give importance on doing things on time)	1–2	1 (1–1.75)	1–3	1 (1–2)	0.008
17 (has initiative)	1–2	1 (1–1)	1–2	1 (1–1)	0.655
18 (has motivation)	1–2	1 (1–1.75)	1–3	1 (1–1)	1.000

Study by Popovic et al. included 67 patients treated with a SSRI in monotherapy for at least six months and similar to our study, participants consisted of patients with a current or lifetime history of MD and patients affected by AD without comorbid MD. The most frequent cognitive complaints were inattentiveness, forgetfulness, mental slowing, apathy, and word-finding difficulty, reported in 15 to 25% of patients and they stated that their findings supported the hypothesis that cognitive symptoms are not simply a result of residual depressive symptomatology which is similar to our findings (17).

Although the etiology of SSRI-induced apathy is largely unknown, some possible mechanisms have been proposed. Firstly, SSRIs may modulate frontal lobe activity via serotonergic systems. Alternatively, the SSRIs may influence serotonergic systems, which modulate midbrain

dopaminergic systems projecting to the prefrontal cortex. Since there is a complex interaction between serotonin, noradrenaline and dopamine systems, activities exerted on serotonin or noradrenaline systems affect dopamine release. 5-HT_{2C} receptor plays a specific role as it phasically and tonically inhibits the basal electrical activity of dopaminergic neurons (18). Considering that the phasic activation of the DA system is associated with motivation and hedonia, serotonergic effects via the 5-HT_{2C} receptor may be particularly relevant in development of SSRI-induced apathy (19). A study by Callegari et al may provide clinical evidence for this proposed mechanism of apathy (20). They studied effects of agomelatine on apathy in a group of patients with frontotemporal dementia. Agomelatine is an antidepressant with agonistic effects on melatonin 1 and 2

receptors and antagonistic effects on 5-HT_{2C} receptor. To tease out the effects of 5-HT_{2C} antagonism, they randomized 24 patients to receive either agomelatine or melatonin for 10 weeks. They reported that agomelatine was associated with a significant reduction of apathy whereas melatonin was not. However, the fact that not all patients develop this syndrome may imply that some other vulnerability factors also play a role, further complicating the attempts to identify the underlying mechanisms (21).

We found that 6 weeks of SSRI treatment was enough to detect emerging apathy. Although current data do not provide a clear guidance about onset of apathy, it is generally considered as a late side effect of SSRIs. However, it is suggested that modifications in brain circuitries secondary to antidepressant administration are already detectable during the first two weeks of treatment. Using magnetic resonance spectroscopy (MRS), Taylor et al. measured N-acetyl-aspartate levels in medial frontal cortex and showed that 7-day escitalopram treatment in depressed patients can produce early changes in neuronal integrity (22). Harmer et al. reported that the reduced recognition of positive facial expressions in MDD was reversed after a single 4-mg dose of the norepinephrine reuptake inhibitor reboxetine (23). Padala et al. (2012) reported 6 cases of SSRI-induced apathy and stated that apathy developed between 2 and 4 months after starting SSRIs in 2 cases, but the timeline for development of apathy was not available in the remaining 4 case (24). Sato and Asada reported a patient with panic disorder who developed apathy one month after the sertraline dose was increased to 50 mg/day (25). These data suggest that emotional side effects may be seen earlier in some individuals, while they appear to be a late phenomenon in some patients, emerging after partial or full recovery from the illness.

There was a significant correlation between AES and HAM-D in our study. In a study evaluating sources of overlap between apathy and depression, Marin et al. determined the correlation between the individual items on the HAM-D and the total scores on the AES and the HAM-D (26). The HAM-D items having the strongest

correlations with AES total score were diminished work/interest, psychomotor retardation, anergy, and lack of insight. Authors attributed the convergence between HAM-D and AES to a subset of HAM-D items which are consistent with the syndrome of apathy and the fact that MD is associated with both apathy and depression. Price et al. reported a similar correlation with a different instrument (Oxford Questionnaire on the Emotional Side-effects of Antidepressants (OQuESA)). They found significant correlations between level of depressive symptoms and OQuESA total score. This shows the challenging nature of distinction between the emotional blunting (e.g., reduced pleasurable emotions, reductions in caring) which arises in the context of depressive disorder and the emotional blunting which may be a side-effect of antidepressant medication. On the other hand, there are also clear differences between these syndromes. Such symptoms as sadness, guilt feelings, self-criticism, helplessness, and hopelessness may help distinguish depression from apathy which is characterized by a lack of emotional responsiveness. In contrast to apathetic individuals who show a lack of concern, self-criticism and negative thoughts about the future are common in depression.

In our study, item-by-item analysis of AES yielded statistically significant increases in 11 of 18 items (1,6 through 11 and 13 through 16). Some of those items overlap with depressive symptoms. However, increasing AES scores in the face of decreasing HAM-D scores suggest that apathetic symptoms follow a different path from underlying depression during the course of treatment. Price et al. conducted a qualitative study with the aim of understanding SSRI-taking patients' experiences of emotional blunting (27). They found that some people taking SSRIs experience significant emotional symptoms that they strongly attribute to their antidepressant. In this study, emotional experiences of patients were described within 6 key themes: general reduction in the intensity of all the emotions, reduction in positive emotions, reduction in negative emotions, emotional detachment, not caring about things and changed personality. Those themes cover some items of AES that we found significant changes with SSRI treatment.

However, it is not possible to make comments about the nature of apathetic symptoms in our patients, since it was not a qualitative study.

Main limitations of this study are small sample size and shorter follow-up period. In addition, the anxiety disorder group was heterogeneous, and the number of patients taking SNRI was too low to allow a comparison with the SSRI group.

Despite limitations, our study is one of the very few studies evaluating SSRI-induced apathy in a naturalistic prospective design. It was evident that after a six-week period of SSRI treatment, apathy level of the patients increased significantly. Clinicians should consider

informing patients who are starting on a course of SSRI treatment about the possibility of apathetic symptoms, such as diminished initiation, poor persistence, lack of interest, indifference, low social engagement and blunted emotional response. Such symptoms should also be monitored by the clinician during routine assessments. Timely interventions addressing SSRI-induced apathy have the potential to improve treatment outcomes.

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