**TABLE. Studies concerning antidepressant-induced apathy syndrome**

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| **Authors** | **Type of study** | **Antidepressant drug inducing apathy & daily dosage** | **Percentage of patients reporting apathy** | **Number of patients & diagnosis** | **Age (years)** | **Gender** | **Measures of apathy** | **Treatment strategy for apathy symptoms** | **Treatment outcome regarding apathy symptoms** | **Comments** |
| Hoehn-Saric et al, 1990 | Case report | Fluoxetine (3 MDD patients; 20 mg)  Fluvoxamine (2 PD patients; 300 and 400 mg/d) | NA | 5  (MDD=3, PD=2) | Mean=43; range= 35-55 | F=4, M=1 | None | Dose-reduction=3; switch to TCA=1; switch to MAOI=1 | Resolved=4; improved=1 | - |
| Hoehn-Saric et al, 1991 | Case report | Fluoxetine (100 mg) | NA | 1  (OCD) | 23 | M | None | Drug discontinuation | Resolved | - |
| George and Trimble, 1992 | Case report | Fluvoxamine (150 mg) | NA | 1  (OCD) | 42 | M | None | Dose reduction | Resolved | - |
| Garland and Baerg, 2001 | Case report | Fluoxetine (N=3; 10, 30 and 40 mg)  Paroxetine (N=2; 20 and 30 mg) | NA | 5  (1 child; 4 adolescents) (OCD=2; MDD=1; ANX-NOS=1; DEPRESS-NOS=1) | Mean=14; range=14-17 | F=2, M=3 | None | Dose reduction=4;  Dose reduction and bupropion (150 mg/d) augmentation=1 | Resolved in all cases | - |
| Marangell et al., 2002 | Open-label clinical trial for the effectiveness of olanzapine in treating SSRI-induced apathy | SSRIs | NA | 21  Non-psychotic MDD in full remission | - | - | AES | Olanzapine 5.4±2.8 mg/d | Significant improvement in all clinical measures | - |
| Opbroek et al., 2002 | Clinical trial | *Number of patients*  Fluoxetine=5; paroxetine=5; sertraline=5  *Mean dosage (mg/d)*  Fluoxetine=40 Paroxetine=26 Sertraline=100  *Mean duration of treatment (months)*  Fluoxetine= 39.2  Paroxetine= 18.8  Sertraline= 22.8 | Apathy symptoms= 80% | 15  (MDD in remission) | 46±11 | F=10, M=5 | LEIS | NA | NA | - |
| Bolling and Kohlenberg, 2004 | Telephone semi-structured interview | SSRIs | “Apathy”= 20%  “Loss of ambition”= 16.1% | Total sample=161 MDD patients who had completed SSRI treatment | - | - | None | NA | NA | - |
| Fava et al., 2006 | Cross-sectional study | Antidepressants | Apathy symptoms=  30-40%; motivation loss= 40%; significant impairment= 12% | 117 (MDD) | 43.4±12.6 | F= 78 (66.7%) | Study-specific clinical measure of AEs | NA | NA | Apathy symptoms may be both drug AEs and MDD residual symptoms |
| Reinblatt and Riddle, 2006 | Case report | Fluvoxamine (N=2; 125 mg) | NA | 2  (GAD+SAD=1; GAD+ SEPAD=1) | 16 and 9 | F=1, M=1 | None | Dose reduction=1; Discontinuation of the drug=1 | Resolved=2 | - |
| Hughes et al., 2007 | Internet-based survey | Duloxetine  Escitalopram  Vilazodone  Vortioxetine | “Emotional numbing”: duloxetine= 8.2%; escitalopram= 10.7%; vilazodone= 4.1% ; vortioxetine= 5.9% | 3243 “users”  Anxiety, depressive, or bipolar disorders. | Half of users: 25-54 | F=1882 (58%); M=794 (24.5%) | Codebook of 60 somatic, emotional and behavioral AEs | NA | NA | - |
| van Geffen et al., 2007 | Internet-based survey of patients and clinicians | SSRIs= 63%, TCA=12%, other antidepressant= 25%  Among all patients, 35% received paroxetine; venlafaxine= 15%; citalopram= 10%; mirtazapine= 8%  Concurrent use of BDZ= 19% | “Apathy"= 10.8% | Total sample=258 | 42.8±13.5 (total sample) | Females= 72%  (total sample) | None | NA | NA | 46% perceived apathy as “very negative”; 54% discontinued treatment.  No clinician traced “apathy” as a side-effect |
| Wongpakaran et al., 2007 | Retrospective case control study using a 10-year database | SSRIs and other antidepressants | Apathy was significantly greater in SSRI-treated elderly | 384 elderly with MDD (90%) and/or dysthymia.  SSRI-treated= 160; non-SSRI-treated= 224 | SSRI-treated: mean= 74.6±6.9  Non-SSRI-treated: mean= 75.7±6.9 | SSRI-treated: F=72.5%;  non-SSRI-treated, F=72.3% | [1] GAS  [2] HAS | NA | NA | Age range 70–75 tends to predict apathy emergence |
| Price et al., 2009 | Qualitative study | SSRIs | NA | 38 patients with MDD or AD and concurrent SSRI-induced apathy | 19-84  (median= 41.5) | F=28, M=10 | None | NA | NA | Data acquired through interviews and from patients’ websites |
| Kodela and Venkata, 2010 | Case report | Sertraline | NA | 1 (MDD) | 48 | M | None | Dose reduction | Resolved | - |
| Goldsmith and Moncrieff, 2011 | Internet-based survey | Mean dose: Fluoxetine= 26.4 mg  Venlafaxine= 145.6 mg | “Emotional blunting”:  venlafaxine= 17%;  fluoxetine= 19% | 468 “users” of venlafaxine (N=182) or fluoxetine | Mean age: fluoxetine= 36.5; venlafaxine= 34.3 | Females: fluoxetine= 73.5%; venlafaxine= 75.8% | None | NA | NA | - |
| Sato and Asada, 2011 | Case report | Sertraline (50 mg) | NA | 1 (PD) | 39 | F | None | Dose reduction (to 25 mg/d) | Resolved | - |
| Padala et al., 2012 | Case report | Citalopram=4; fluoxetine=2 | NA | 6 MDD patients | Range= 53-76 | M=6 | AES-C | SSRI discontinuation without or with (N=2) bupropion administration | Significant improvement in all cases | - |
| Raskin et al., 2012 | Multicenter, double-blind, randomized 8-week study | SSRIs (citalopram, escitalopram, paroxetine, sertraline) and other antidepressants | NA | 483  MDD in remission, but with apathy symptoms | Median age: duloxetine= 45.1; escitalopram= 45.0 | Females: duloxetine= 76.6%; escitalopram= 74.9% | AES-C | Switch to duloxetine (244) or escitalopram (179)  Remain to escitalopram=60 | Similar reductions of apathy with the two switch-strategies  Reductions of apathy also in patients who remained on escitalopram | Switching to SSRI or SNRI were equally effective to treat apathy |
| Corruble et al., 2013 | Randomized, controlled, 24-week, double-blind trial | Agomelatine  (25-50 mg/d)    Escitalopram  (10-20 mg/d) | “Emotions lack intensity”: agomelatine= 28% vs escitalopram= 60% | Agomelatine= 25  Escitalopram= 20 | Agomelatine= 43.6±12.9  Escitalopram= 42.8±11.8 | Females: agomelatine= 73.2%; escitalopram= 68.7% | OQESA | NA | NA | Agomelatine superior to escitalopram concerning apathy emergence |
| De Berardis et al., 2013 | Case report | Escitalopram  (10 mg) | NA | 1 (MDD) | 70 | M | AES | Co-administration of agomelatine 25 mg/d | Resolved | Escitalopram was discontinued within 9 weeks |
| Read et al., 2014; Cartwright et al., 2016 | Internet-based survey | Fluoxetine= 22.4%; citalopram= 20.3%; paroxetine 8.7%; TCAs= 4.5%; venlafaxine= 2.2%; multiple antidepressants 39% | “Feeling Emotionally Numb”= 60%; “Reduction in Positive Feelings”= 42%; “Caring Less About Others”= 39% | 1829 “users” of antidepressants | Mean age group= 36-45 | Females= 76.6% | Study-specific questionnaire of antidepressant AEs | NA | NA | - |
| Popovic et al., 2015 | Clinical study | SSRIs  (Paroxetine, citalopram, escitalopram, fluoxetine, sertraline) | Apathy symptoms:  All patients=  20.4%.  MDD= 22.6%  AD= 18.2% | 67  MDD=37  AD=30 | Mean age:    MDD= 47.3  AD= 39.5 | Males= 46.3% | Study-specific questionnaire | NA | NA | - |
| Goodwin et al., 2017 | Internet-based survey | *Monotherapy* with:  [1] *SSRIs*: Sertraline, fluoxetine, paroxetine, escitalopram, citalopram.  [2] *non-SSRI antidepressants:* duloxetine, mirtazapine, venlafaxine, bupropion, desvenlafaxine, amitriptyline. | 46% of currently depressed patients had emotional blunting (men= 52%, women= 44%) | 669 with current MDD on treatment and 150 drug-free previously depressed controls | With emotional blunting= 49.5±12.3;  Without emotional blunting= 51.7±12.4 | With emotional blunting: females= 68%  Without emotional blunting: females= 75% | OQESA | NA | NA | *No significant difference of apathy* according to antidepressant agent.  Positive correlation between OQESA and HAMD scores. |
| Kajanoja et al., 2018 | Clinical study | Serotoninergic antidepressants | Patients  on  medication  had greater  difficulty  to identify  feelings | 57 MDD patients  441 controls | - | - | TAS-subscale: “difficulty identifying feelings” | NA | NA | - |
| Read and Williams, 2018 | Internet-based survey | Antidepressants | “Feeling emotionally numb”= 71%  “Reduction in positive feelings”= 60%  “Caring less about others”= 54.5% | 1.431 users of antidepressants  (from 38 countries) | - | - | Questionnaire with 20 AEs of antidepressants including apathy symptoms | NA | NA | Less than 5% of the patients were informed at baseline for potential side effects  . |
| Kim et al., 2019 | Case report | Dosages (mg/d):  Fluoxetine= 60, venlafaxine= 225, mirtazapine= 30, aripiprazole= 5 | NA | 1 (MDD) | 67 | F | AES | Discontinuation of all antidepressants.  Administration of methylphenidate (25 mg/d), modafinil (200 mg/d) and olanzapine (10 mg/d) | Resolved | - |
| Ascibasi et al., 2020 | Prospective clinical study | SSRI= 41.8%; SNRI= 40.8%; vortioxetine= 13.3%; others= 4.1% | NA  (Focus on the association of apathy and depressive symptoms) | 98 (MDD) | 34.9±10.6 | F=70.4% | OQESA | NA | NA | The OQESA scores were related both to drug AEs and to residual MDD symptoms |
| Padala et al., 2020 | Retrospective chart review study | SSRIs (citalopram, escitalopram, paroxetine, fluoxetine, sertraline) | Apathy:  SSRI-treated patients= 92%; non-SSRI treated= 61% | 119  (MDD, bipolar disorder, anxiety disorders, schizophrenia, schizoaffective disorder, dementia) | SSRI-treated= 57.2±15.4  Non-SSRI-treated= 54.2±11.5 | Not mentioned (“the majority were males”) | AES-C | NA | NA | - |
| Read et al., 2020 | Internet-based survey | Antidepressants | “Emotional blunting”= 5.8% | 342 users of antidepressant drugs | - | - | List of open questions concerning users’ experience with antidepressants | NA | NA | - |
| Sato et al., 2020 | Case report | Venlafaxine | Mild apathy at 75 and 37.5 mg/d respectively | 2 | 47 and 55 | Males | None | Increase of venlafaxine to 150 mg/d (both) | Resolved (both) | Apathy was attributed to the serotoninergic component of venlafaxine |
| Camino et al., 2022 | Analysis of data from patient-oriented website | *Dosage (mg) (SD):*  Sertraline= 93.5 (53.9)  Paroxetine= 31.3 (15.9)  Fluoxetine= 32.9 (18.6)  Escitalopram= 14.1 (7.3)  Citalopram= 30.2 (16.6)  Venlafaxine= 139.6 (141.0)  Duloxetine= 75.4 (37.4)  Mirtazapine= 31.1 (17.4)  Bupropion= 270 (89.2) | Total percentage of users reporting “emotional blunting”=18%  Sertraline=26%  Paroxetine=32% Fluoxetine=24%  Escitalopram= 18%  Citalopram= 14%  Venlafaxine= 12.5%  Duloxetine= 22%  Mirtazapine= 9.8%  Bupropion= 4% | 50 posts for each antidepressant (total=450)  MDD= 66.7%  Bipolar disorder= 4.7%  Anxiety disorder= 51%  OCD= 7% | Median age=37; IQR=26.25-49.00 | Females= 70.2%  Males=29.8% | NA | NA | NA | - |
| Christensen et al., 2022 | Internet-based survey of MDD patients in acute or remission phase, currently receiving a prescribed antidepressant, who reported emotional blunting during the last 6 weeks | *Antidepressant received by patients:* Fluoxetine 26%; escitalopram 17%; sertraline 16%; citalopram 15%; venlafaxine 13%; bupropion 11%; paroxetine 10%; duloxetine 7%; mirtazapine 6%; desvenlafaxine 5%; vortioxetine 4%; agomelatine 3%; other drug therapy 23% | Only patients with apathy were included in the study  Patients rating their emotional blunting as “extremely severe”=44%  Patients attributing their emotional blunting to: [a] the MDD=56%; [b] the antidepressant drug=45%  1/3 of patients were considering stopping or had stopped the medication as a result | 752 MDD patients in acute (N=300) or remission phase (N=452) | 45 (SD=12) | Female=62%  Male=38% | ODG | NA | NA | - |

**Abbreviations: AD=** anxiety disorder; **AEs=** adverse effects; **AES=** Apathy Evaluation Scale; **AES-C=** Apathy Evaluation Scale-Clinical Version; **ANX-NOS=** anxiety disorder not otherwise specified; **AS=** Apathy Scale; **BDZ=** benzodiazepine; **DEPRESS-NOS=** depressive disorder not otherwise specified; **F=** female; **GAD=** generalized anxiety disorder; **GAS=** GDS-apathy subscale; **GDS=** Geriatric Depression Scale; **CGI-S=** Clinical Global Impressions-Severity of Illness scale; **HAMD=** Hamilton Rating Scale for Depression; **HAS=** HAMD-apathy subscale; **IQR=** Interquartile range; **M=** male; **LEIS=** Laukes Emotional Intensity Scale; **MADRS=** Montgomery-Asberg Depression Rating scale; **MAOI=** monoamine oxidase inhibitor; **MDD=** major depressive disorder; **NA=** non-applicable (e.g. when all patients are selected to suffer from drug-induced apathy); **OCD=** obsessive-compulsive disorder; **ODQ=** Oxford Depression Questionnaire; **OQESA=** Oxford Questionnaire on the Emotional Side-effects of Antidepressants; **PD**= panic disorder; **SAD=** social anxiety disorder; **SD=** Standard Deviation; **SEPAD=** separation anxiety disorder; **SSRI=** selective serotonin reuptake inhibitor; **TAS=** Toronto Alexithymia Scale; **TCA=** tricyclic antidepressant.