*Acta Neuropsychiatrica*

**cambridge.org/neu**

# Apathy associated with antidepressant drugs: a systematic review

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**Review Article**

**Cite this article:** Masdrakis VG, Markianos M, and Baldwin DS. (2023) Apathy associated with antidepressant drugs: a systematic review. *Acta Neuropsychiatrica* **35**:189–204.
doi: 10.1017/neu.2023.6

Received: 14 October 2022
Revised: 3 January 2023
Accepted: 3 January 2023
First published online: 16 January 2023

**Key words:**
antidepressant drugs; apathy syndrome; emotional blunting; selective serotonin reuptake inhibitors

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## Abstract

*Objectives:* Administration of antidepressant drugs – principally selective serotonin reuptake inhibitors (SSRIs) – may induce clinically significant 'apathy' which can affect treatment outcomes adversely. We aimed to review all relevant previous reports. *Methods:* We performed a PUBMED search of English-language studies, combining terms concerning psychopathology (e.g. apathy) and classes of antidepressants (e.g. SSRI). *Results:* According to certain inclusion (e.g. use of DSM/ICD diagnostic criteria) and exclusion (e.g. presence of a clinical condition that may induce apathy) criteria, 50 articles were eligible for review. Together, they suggest that administration of antidepressants – usually SSRIs – can induce an apathy syndrome or emotional blunting, i.e. a decrease in emotional responsiveness, to circumstances which would have triggered intense mood reactions prior to pharmacotherapy. The reported prevalence of antidepressant-induced apathy ranges between 5.8 and 50%, and for SSRIs ranges between 20 and 92%. Antidepressant-induced apathy emerges independently of diagnosis, age, and treatment outcome and appears dose-dependent and reversible. The main treatment strategy is dose reduction, though some data suggest the usefulness of treatment with olanzapine, bupropion, agomelatine or amisulpride, or the methylphenidate–modafinil–olanzapine combination. *Conclusion:* Antidepressant-induced apathy needs careful clinical attention. Further systematic research is needed to investigate the prevalence, course, aetiology, and treatment of this important clinical condition.

## Summations

- Pharmacotherapy with antidepressants (mostly SSRIs) may induce an array of clinically significant manifestations, collectively termed 'apathy syndrome' or 'emotional blunting'. Its estimated prevalence ranges from 5.8% to almost 50%, but in samples treated only with SSRIs may range between 20% and 92%.
- Antidepressant-induced apathy emerges independently of the psychiatric disorder for which the drug is prescribed and is found in all age groups. It is independent of treatment outcome and may be clinically present even after psychopathology has remitted.

## Considerations

- There is a paucity of clinical trials, especially randomised placebo-controlled ones. Most studies are either case reports or internet/telephone surveys in samples of 'users' of antidepressant medications.
- In many of the relevant reports, non-specific clinical measures – or no measures at all – are used to evaluate apathy symptoms.
- The retrospective nature of many reports cannot exclude the possibility that patients were being treated with SSRIs rather than with other antidepressants because of accompanying factors which may also have influenced apathy.

## Introduction

In patients with depressive, anxiety, or other psychiatric disorders, pharmacotherapy with antidepressants [mostly with selective serotonin reuptake inhibitors (SSRIs), but sometimes with antidepressants from other classes] may induce an array of clinically significant manifestations, collectively termed '*apathy syndrome*' or '*emotional blunting*' (or the narrower term '*inability to*

*cry*') (e.g. Hoehn-Saric *et al.*, 1990; Hoehn-Saric *et al.*, 1991; George & Trimble, 1992; Garland & Baerg, 2001; Barnhart *et al.*, 2004).

Observed or reported features include a decrease in emotional responsiveness to circumstances which would have triggered intense mood reactions prior to pharmacotherapy. 'Antidepressant-induced apathy' often emerges soon after starting pharmacotherapy and may significantly compromise both treatment outcome and quality of life (Padala *et al.*, 2020). Differential diagnosis is often difficult, as apathy symptoms are included in the clinical presentation of other neurological and psychiatric conditions (e.g. traumatic brain injury, dementia, cannabis use) (Barnhart *et al.*, 2004). Additionally, apathy symptoms may be either a residual feature of the clinical condition for which the medication is administered or an early manifestation of relapse (Kelly *et al.*, 2008).

As such, data concerning the clinical presentation, differential diagnosis, and treatment of antidepressant-induced apathy are important for everyday clinical practice of mental health professionals. Review papers regarding this issue have been previously published, but the most recent was published in 2010 and concerns only SSRI-induced apathy (Barnhart *et al.*, 2004; Sansone & Sansone, 2010; Lee & Keltner, 2005). A more recent review included consideration of treatment-associated apathy within a broader account of many potential adverse effects of SSRIs only (Marazziti *et al.*, 2019).

We aimed to investigate in a systematic fashion all publications regarding apathy/emotional blunting manifestations in patients undergoing pharmacotherapy with any antidepressant agent.

## Method for the literature review

### *Criteria for the appraisal of quality of reports*

We conducted a search through PUBMED to investigate previous reports which have explored various aspects (clinical features, treatment strategies, etc.) of antidepressant-induced apathy syndrome. A number of inclusion and exclusion criteria were specified to decide whether to include a report in our review.

#### *Inclusion criteria*

(1) Only publications in scientific journals with a peer-review process were included and (2) diagnoses were based on criteria from standard international diagnostic systems (i.e. DSM, ICD).

#### *Exclusion criteria*

(1) Comorbid neurological or other somatic diseases that can cause apathy manifestations and (2) comorbid alcohol/substance use disorder.

### *Search methodology*

In the PUBMED search, we combined the terms 'apathy' (sub-section 'Apathy'), 'crying' (sub-section 'Crying'), and 'emotional blunting' (sub-section 'Emotional blunting') with various terms concerning classes of antidepressant medications, for example, 'selective serotonin reuptake inhibitors', 'tricyclic antidepressants', etc. In all cases, the last day of PUBMED search was 11th July 2022. Only English-language studies were reviewed.

#### *Apathy*

We performed an updated PUBMED search using the terms ('apathy', **OR** 'apathy syndrome') **AND** ('selective serotonin reuptake inhibitors', **OR** 'SSRIs', **OR** 'serotonin noradrenaline reuptake inhibitors', **OR** 'SNRIs', **OR** 'tricyclic antidepressants', **OR** 'TCAs', **OR** 'antidepressants').

More precisely, the following combinations of terms were explored in the PUBMED (in brackets ***N*** = the total number of papers that the respective search yielded and ***E*** = the number of articles that were deemed eligible to be included, according to inclusion/exclusion criteria *and after removing the duplications from the previous PUBMED search/searches*): (1) 'apathy + selective serotonin reuptake inhibitors' ($N = 88$, $E = \mathbf{20}$); (2) 'apathy + SSRIs' ($N = 83$, $E = \mathbf{2}$); (3) 'apathy syndrome + selective serotonin reuptake inhibitors' ($N = 29$, $E = \mathbf{3}$); (4) 'apathy syndrome + SSRIs' ($N = 24$, $E = 0$); (5) 'apathy + serotonin noradrenaline reuptake inhibitors' ($N = 11$, $E = \mathbf{1}$); (6) 'apathy + SNRIs' ($N = 11$, $E = 0$); (7) 'apathy syndrome + serotonin noradrenaline reuptake inhibitors' ($N = 2$, $E = 0$); (8) 'apathy syndrome + SNRIs' ($N = 2$, $E = 0$); (9) 'apathy + tricyclic antidepressants' ($N = 2$, $E = 0$); (11) 'apathy + TCAs' ($N = 1$, $E = 0$); (10) 'apathy syndrome + tricyclic antidepressants' ($N = 10$, $E = 0$); (12) 'apathy syndrome + TCAs' ($N = 1$, $E = 0$); (13) 'apathy + antidepressants' ($N = 63$, $E = \mathbf{4}$); and (14) 'apathy syndrome + antidepressants' ($N = 63$, $E = \mathbf{1}$).

Consequently, the total number of papers that were deemed eligible to be included in the review was **31** (Hoehn-Saric *et al.*, 1990; Hoehn-Saric *et al.*, 1991; George & Trimble, 1992; Garland & Baerg, 2001; Barnhart *et al.*, 2004; Padala *et al.*, 2020; Kelly *et al.*, 2008; Sansone & Sansone, 2010; Lee & Keltner, 2005; Szmulewicz *et al.*, 2016; Padala *et al.*, 2012; Goodwin *et al.*, 2017; Sato *et al.*, 2020; Fava *et al.*, 2006; Popovic *et al.*, 2015; Rothschild *et al.*, 2014; Reinblatt & Riddle, 2006; Kodela & Venkata, 2010; De Berardis *et al.*, 2013; Kim *et al.*, 2019; Marangell *et al.*, 2002; Bolling & Kohlenberg, 2004; Settle, 1998; Cassano & Fava, 2004; van Geffen *et al.*, 2007; Wongpakaran *et al.*, 2007; Sato & Asada, 2011; Raskin *et al.*, 2012; Read *et al.*, 2014; Carvalho *et al.*, 2016; Ascibasi *et al.*, 2020).

Included in these 31 articles were 5 reviews which generally investigated pharmacotherapy with SSRIs/antidepressants and adverse events with these medications (Kelly *et al.*, 2008; Szmulewicz *et al.*, 2016; Settle, 1998; Cassano & Fava, 2004; Carvalho *et al.*, 2016) and 3 reviews which explored the emergence of apathy during pharmacotherapy with SSRIs or other antidepressants (Barnhart *et al.*, 2004; Sansone & Sansone, 2010; Lee & Keltner, 2005).

#### *Crying*

We performed an updated PUBMED search using the terms ('crying') **AND** ('selective serotonin reuptake inhibitors', **OR** 'SSRIs', **OR** 'serotonin noradrenaline reuptake inhibitors', **OR** 'SNRIs', **OR** 'tricyclic antidepressants', **OR** 'TCAs', **OR** 'antidepressants').

More precisely, the following combinations of terms were explored in the PUBMED (in brackets ***N*** = the total number of papers that the respective search yielded and ***E*** = the number of articles that were deemed eligible to be included in the review, according to inclusion/exclusion criteria and *after removing the duplications from the previous PUBMED search/searches concerning both 'crying' and 'apathy'*): (1) 'crying + selective serotonin reuptake inhibitors' ($N = 67$, $E = \mathbf{5}$); (2) 'crying + SSRIs' ($N = 57$, $E = 0$); (3) 'crying + serotonin noradrenaline reuptake inhibitors' ($N = 4$, $E = 0$); (4) 'crying + SNRIs' ($N = 4$, $E = 0$); (5) 'crying + tricyclic antidepressants' ($N = 28$, $E = 0$); (6) 'crying + TCAs' ($N = 3$, $E = 0$); and' (7) 'crying + antidepressants' ($N = 144$, $E = \mathbf{1}$).

Consequently, the total number of papers that were deemed eligible to be included in the present review was **6** (Scoppetta *et al.*,

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2005; Opbroek *et al*., 2002; Oleshansky & Labbate, 1996; Vinar, 2000; van der Veen *et al*., 2012; Holguin-Lew & Bell, 2013).

### *Emotional blunting*

We performed an updated PUBMED search using the terms ('emotional blunting') **AND** ('selective serotonin reuptake inhibitors', **OR** 'SSRIs', **OR** 'serotonin noradrenaline reuptake inhibitors', **OR** 'SNRIs', **OR** 'tricyclic antidepressants', **OR** 'TCAs', **OR** 'antidepressants').

More precisely, the following combinations of terms were explored in the PUBMED (in brackets ***N*** = the total number of papers that the respective search yielded and ***E*** = the number of articles that – among the *N* articles – were deemed eligible to be included, according to inclusion/exclusion criteria and *after removing the duplications from the previous PUBMED search/searches concerning 'emotional blunting', 'crying' and 'apathy'*): (1) 'emotional blunting + selective serotonin reuptake inhibitors' ($N = 51$, $E = \mathbf{4}$); (2) 'emotional blunting + SSRIs' ($N = 48$, $E = 0$); (3) 'emotional blunting + serotonin noradrenaline reuptake inhibitors' ($N = 6$, $E = 0$); (4) 'emotional blunting + SNRIs' ($N = 5$, $E = 0$); (5) 'emotional blunting + tricyclic antidepressants' ($N = 9$, $E = 0$); (6) 'emotional blunting + TCAs' ($N = 1$, $E = 0$); and (7) 'emotional blunting + antidepressants' ($N = 107$, $E = \mathbf{9}$).

Consequently, the total number of papers that were deemed eligible to be included in the present review was **13** (Price *et al*., 2009; Price *et al*., 2012; Goldsmith & Moncrieff, 2011; Balon, 2002; Corruble *et al*., 2013; Cartwright *et al*., 2016; Hughes *et al*., 2017; Kajanoja *et al*., 2018; Read & Williams, 2018; Marazziti *et al*., 2019; Read *et al*., 2020; Camino *et al*., 2022; Christensen *et al*., 2022). Included in these 13 articles is one review paper concerning adverse effects – including emotional blunting – of SSRIs only (Marazziti *et al*., 2019).

## Results

Overall, the updated PUBMED search using various combinations of terms yielded a total of **50** articles to be included in the present review (for the references, see sub-section 'Search methodology'). More data (e.g. patients' age, dosages, etc.) regarding the studies that are described in this section can be found in Table 1. Additionally, the terms 'apathy' and 'emotional blunting' are used interchangeably, in line with previous reports.

Based on the data of these 50 studies, in the following sub-sections we refer to the definition, clinical features, differential diagnosis, and prevalence of antidepressant-induced apathy syndrome (sub-section 'Antidepressant-induced apathy syndrome: definition, clinical features, differential diagnosis, and prevalence'), in its aetiology and treatment (sub-section 'Aetiology and treatment'), while in the final sub-section 'Clinical trials, case reports, and internet/telephone surveys' we refer in more detail to data from previous relevant reports.

### *Antidepressant-induced apathy syndrome: definition, clinical features, differential diagnosis, and prevalence*

#### *Definition and clinical presentation*

'*Apathy syndrome'* is defined as the syndrome whose main clinical characteristic is a primary loss of motivation which is not due to any intellectual impairment, emotional distress, or decreased consciousness (Marin *et al*., 1991).

In patients with depressive, anxiety, or other psychiatric disorders, pharmacotherapy with antidepressants (principally with SSRIs, but sometimes with antidepressants from other classes) may induce an array of clinically significant manifestations, collectively termed '*apathy syndrome'* or '*emotional blunting'* (or the more narrow term '*inability to cry*') (e.g. Hoehn-Saric *et al*., 1990; Hoehn-Saric *et al*., 1991; George & Trimble, 1992; Garland & Baerg, 2001; Barnhart *et al*., 2004; Padala *et al*., 2020). These manifestations often have an insidious onset and include lack of motivation or dullness and, more generally, a decrease in emotional responsiveness to circumstances which would have triggered intense mood reactions before antidepressant treatment had started. Antidepressants not only alleviate depressive symptoms but may also 'attenuate' or 'set aside everyday concerns' (Kelly *et al*., 2008; Sansone & Sansone, 2010; Szmulewicz *et al*., 2016).

This decreased responsiveness involves many aspects of emotions, including crying, irritation, sadness, and creativity (Scoppetta *et al*., 2005). It has been suggested that the well-known effect of SSRI on sexual desire and interest may be a concomitant and potential marker of the apathy syndrome induced by these medications (Sansone & Sansone, 2010; Szmulewicz *et al*., 2016; Opbroek *et al*., 2002).

Antidepressant-induced apathy appears both *dose-dependent* and *reversible* (Padala *et al*., 2020). Patients can often differentiate between loss of interest as a symptom of depression from the apathy associated with SSRI treatment (Hoehn-Saric *et al*., 1990; Barnhart *et al*., 2004). However, apathy symptoms are frequently not reported and often remain untreated, with subsequent clinical, social, and professional consequences. A proportion of patients may consider antidepressant-induced apathy to be beneficial, but probably most consider them to be the cause of difficulties such as financial and working problems (Price *et al*., 2009).

Apathy manifestations often emerge soon after an antidepressant is started and are most frequently reversible after drug discontinuation, and their emergence does not appear associated with patients' age or diagnosis (Padala *et al*., 2020). In particular, the onset of apathy with SSRIs use may be very quick. Thus, in a functional magnetic resonance imaging study in a sample of healthy volunteers, 1 week of citalopram administration was associated with reduction in activity in the reward networks of ventral striatum and ventral medial/orbitofrontal cortex (McCabe *et al*., 2010). Some data suggest that apathy emergence is an effect specific to SSRIs administration, as apathy manifestations during treatment with SSRIs can remit after switching to an antidepressant from another class (Hoehn-Saric *et al*., 1990; Hoehn-Saric *et al*., 1991; Padala *et al*., 2012). However, an internet-based survey in patients with major depressive disorder (MDD) found no difference regarding the prevalence of emotional blunting with differing antidepressant medicines (including SSRIs, SNRIs, mirtazapine, bupropion, and amitriptyline), though it appeared less evident with bupropion (Goodwin *et al*., 2017). More recently, Sato *et al* (2020) reported two cases of venlafaxine-induced apathy but attributed it to the serotoninergic component of the drug. More details regarding the above-mentioned studies are included in sub-section 'Clinical trials, case reports, and internet/telephone surveys'.

Antidepressant-induced apathy appears independent of the psychiatric disorder for which medication is prescribed and has been found in all age groups of patients with depressive or anxiety disorders (see for a review: Szmulewicz *et al*., 2016). Antidepressant-induced apathy also seems to be independent of treatment outcome and may be clinically present even after depressive and anxiety symptoms have remitted (Fava *et al*., 2006; Popovic *et al*., 2015). Importantly, some clinicians consider violent

https://doi.org/10.1017/neu.2023.6 Published online by Cambridge University Press

**Table 1.** Studies concerning antidepressant-induced apathy syndrome

| Authors | Type of study | Antidepressant drug inducing apathy and daily dosage | Percentage of patients reporting apathy | Number of patients and 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/day) | 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/day | 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 | – |

**Table 1.** (*Continued*)

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 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.* (2017) | 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 behavioural 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 |

(*Continued*)

**Table 1.** (*Continued*)

| Authors | Type of study | Antidepressant drug inducing apathy and daily dosage | Percentage of patients reporting apathy | Number of patients and diagnosis | Age (years) | Gender | Measures of apathy | Treatment strategy for apathy symptoms | Treatment outcome regarding apathy symptoms | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 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/day) | 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) | Multicentre, double-blind, randomised 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) | Randomised, controlled, 24-week, double-blind trial | Agomelatine (25–50 mg/day); Escitalopram (10–20 mg/day) | '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 |

**Table 1.** (*Continued*)

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 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. |

(*Continued*)

**Table 1.** (*Continued*)

| Authors | Type of study | Antidepressant drug inducing apathy and daily dosage | Percentage of patients reporting apathy | Number of patients and diagnosis | Age (years) | Gender | Measures of apathy | Treatment strategy for apathy symptoms | Treatment outcome regarding apathy symptoms | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 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/day), modafinil (200 mg/day) and olanzapine (10 mg/day) | 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/day, 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 |

**Table 1.** (*Continued*)

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 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 | – |

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, generalised 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.

behaviour in SSRI-treated adolescents to be related, at least in part, to the experience of medication-induced apathy (Lee & Keltner, 2005).

### *Differential diagnosis and clinical measures of apathy*

Clinicians must take into account that apathy manifestations are included in the clinical presentation of other medical conditions, such as (apathetic) hyperthyroidism, dementia, frontal lobe lesions, and cannabis use (Barnhart *et al.*, 2004). Additionally, apathy symptoms may be an adverse effect of medication, a residual symptom, or an early manifestation of relapse (Kelly *et al.*, 2008). It has been suggested that the presence of apathy without concurrent fatigue is more indicative that it is antidepressant-induced (Barnhart *et al.*, 2004). Although the symptoms of apathy and depression overlap, they are considered distinct clinical entities (Levy *et al.*, 1998; Monga & Padala, 2015). Patients with apathy can demonstrate a lack of concern, while depressed patients show pathological self-criticism and a negative outlook – two symptoms which are usually absent in apathy (Landes *et al.*, 2001). Furthermore, at a nosological level, it is considered important to define the exact relationship between apathy and anhedonia – the latter defined as the (complete) inability to experience pleasure, as manifested in facial expression, speech, behaviour, lifestyle, and the individual's account of personal experience. Thus, Starkstein and Leentjens (2008) emphasise that this relationship depends on how apathy is conceptualised. If apathy is considered a state of absence of feeling and emotional sensitivity, anhedonia should be considered a mandatory symptom of apathy. If, on the other hand, apathy is considered a state of diminished motivation, anhedonia may not be a necessary diagnostic criterion.

As it is often difficult to trace apathy manifestations and differentiate them from depressive symptoms, a number of clinical measures have been developed for this purpose, including the Apathy Evaluation Scale (Marin *et al.*, 1991), the Rothschild Scale for Antidepressant Tachyphylaxis (RSAT) (Rothschild *et al.*, 2014; Rothschild, 2008), the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) (Rothschild *et al.*, 2014; Fava *et al.*, 2009), and the Oxford Questionnaire on the Emotional Side effects of Antidepressants (OQESA) (Price *et al.*, 2012). Most recently, novel clinical evaluation methods combining text, audio, and video features were used for the early detection and differential diagnosis of apathy and depression in patients with mild cognitive impairment (Zhou *et al.*, 2022). Of note, clinical measures must be part of a broader, comprehensive neuropsychiatric evaluation, including the assessment of patient's social and physical context, her/his education, social class, interests and goals, and cultural parameters (Marin & Wilkosz, 2005).

### *Prevalence*

The prevalence of antidepressant-induced apathy may be high. An early study found that up to 80% of 15 patients with SSRI-induced sexual dysfunction also reported clinically significant emotional blunting (Opbroek *et al.*, 2002). Goodwin *et al* (2017) reported that among 669 MDD patients undergoing monotherapy with either an SSRI (citalopram, escitalopram, fluoxetine, paroxetine, or sertraline) or a non-SSRI-antidepressant (amitriptyline, bupropion, desvenlafaxine, duloxetine, mirtazapine, or venlafaxine), the overall prevalence of emotional blunting was 46%. A retrospective chart review of 125 outpatients receiving only SSRIs found that up to 92% demonstrated clinically significant apathy (Padala *et al.*, 2020). Regarding paediatric populations, 5% of 45 patients with anxiety disorders receiving the SSRI fluvoxamine demonstrated apathy symptomatology, without concomitant depression (Reinblatt & Riddle, 2006). More data about the prevalence of antidepressant-induced apathy are mentioned in sub-section 'Clinical trials, case reports, and internet/telephone surveys'.

## *Aetiology and treatment*

### *Aetiology*

The mechanisms underlying the syndrome are not clarified fully. Due to the effect of SSRIs on pathological emotional lability, a serotoninergic hypothesis has been proposed: SSRIs may exert their therapeutic effect by elevating the 'threshold' for feeling intense emotions and subsequently by reducing emotional 'responsiveness' (Scoppetta *et al.*, 2005). As clinically similar emotional blunting can be observed after damage to the anterior cingulate cortex, which receives extensive dopaminergic input from the ventral tegmental area, abnormal dopaminergic activity is also conjectured to be a cause of apathy (Padala *et al.*, 2020). Furthermore, in healthy subjects, an inverse association was found between 'crying proneness' (as reflected in the 'crying easily'-item of the Symptom Checklist-90 measure) and cerebrospinal fluid levels of the noradrenaline metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG), suggesting that central noradrenergic mechanisms may contribute to crying behaviour (Markianos *et al.*, 2001).

Hoehn-Saric *et al* (1990, 1991) proposed two alternative mechanisms. The first is that SSRIs directly modulate frontal lobe activity through changes in serotoninergic systems. Alternatively, SSRI administration may alter serotoninergic systems and subsequently modulate midbrain dopaminergic systems which project to the prefrontal cortex: that is, SSRIs indirectly modulate frontal lobe activity by inhibiting the release of dopamine. In this respect, agonism of $5HT_{-2C}$ receptors may play a particular role (Gobert *et al.*, 2002; Arnone *et al.*, 2009). More precisely, SSRI-induced chronic increases of serotonin levels in the nucleus accumbens leads – due to $5HT_{-2C}$ agonism – may lead to a down-regulation of dopamine turn-over in neurobiological structures closely associated with apathy. The subsequent SSRI-induced 'frontal hypo-dopaminergic' state may manifest as apathy (Hoehn-Saric *et al.*, 1990; Hoehn-Saric *et al.*, 1991; Lee & Keltner, 2005; Szmulewicz *et al.*, 2016; Levy & Dubois, 2006).

Emotional blunting may reduce a focus on depressed feelings or negative experiences (Harmer *et al.*, 2004). Moncrieff and Cohen (2005, 2006) have proposed that antidepressants work through a 'drug-centred' mechanism, altering a patient's mental state which subsequently impacts MDD psychopathology, rather than through a 'disease-centred' way, that is, by reversing specific biological mechanisms underlying disease.

SSRIs may alter neurocognitive processes underlying recognition of an array of emotions, including happiness, sadness, fear, disgust, and surprise, both in MDD patients and in healthy controls (Harmer *et al.*, 2004; Harmer *et al.*, 2011). Some researchers suggest antidepressants with a different mechanism of action – such as reboxetine (Harmer *et al.*, 2004), mirtazapine (Arnone *et al.*, 2009), or agomelatine (Harmer *et al.*, 2011) – may modify biological factors underlying the processing of happiness and sadness, but not of other emotions. However, further evidence is needed concerning this hypothesis.

### *Treatment options*

*Dose reduction of the antidepressant.* Since apathy can be a residual symptom of depression, the clinician may consider increasing the dose of the antidepressant: however, if apathy was

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not part of the manifestations of MDD prior to antidepressant treatment, then apathy is possibly an adverse effect of the pharmacotherapy, in which case a dose reduction may be preferred (Padala *et al*., 2012; Kodela & Venkata, 2010). It has been suggested that if a differential diagnosis cannot be made, a first step is to increase the daily dosage: if symptoms are due to drug-induced apathy and not to MDD, they are expected to worsen, in which case the clinician can safely reduce the dosage (Lee & Keltner, 2005): with this strategy a clinician might avoid a potential relapse of MDD, if they reduce the antidepressant dosage mistakenly assuming it is apathy syndrome – but the evidence for this suggested approach is very limited.

*Pharmacotherapy of antidepressant-induced apathy.* Relevant data are limited to cases treated with bupropion (Garland & Baerg, 2001), agomelatine (De Berardis *et al*., 2013), amisulpride (Monga & Padala, 2015), and a methylphenidate-modafinil-olanzapine combination (Kim *et al*., 2019), together with an open-label study of olanzapine administration (Marangell *et al*., 2002) (for details, see sub-section 'Clinical trials, case reports, and internet/telephone surveys' and Table 1).

*Considering antidepressant-induced apathy as a beneficial effect.* Many patients dislike antidepressant-induced emotional suppression or disengagement, especially since these manifestations are often associated with other side effects, such as decline in sexual interest and function (Bolling & Kohlenberg, 2004; Price *et al*., 2009; Goldsmith & Moncrieff, 2011). However, some patients seem to consider this 'emotional numbing' as a desired effect, helping to overcome often intense symptoms of affective disorders and/or providing some relief from psychosocial stressors (Hoehn-Saric *et al*., 1990; Lee & Keltner, 2005; Price *et al*., 2009; Moncrieff, 2015).

## Clinical trials, case reports, and internet/telephone surveys

In each of the following sub-sections ('Clinical trials', 'Case reports', and 'Internet/telephone surveys and investigation of patient-oriented websites'), studies are reviewed in chronological order: for reports from the same year, alphabetical order is followed.

### Clinical trials

An open-label study explored the effectiveness of olanzapine for treatment of prominent apathy in the absence of depression in 21 patients with non-psychotic MDD in full remission, all receiving long-term pharmacotherapy with an SSRI (Marangell *et al*., 2002). The rationale for adding olanzapine to SSRI treatment was that it can enhance dopamine availability in the frontal cortex by blocking serotonin-induced inhibition of dopamine release. Following initial response, olanzapine was administered for 8 weeks at a stable dose (5.4 ± 2.8 mg/day). Clinically significant improvements were seen in all measures of apathy.

In a clinical trial, up to 80% of 15 patients with SSRI (fluoxetine, paroxetine, or sertraline)-induced sexual dysfunction also reported clinically significant apathy, including reductions regarding ability to cry, irritation, care about others' feelings, sadness, erotic dreaming, creativity, surprise, anger, expression of their feelings, worry over things or situations, sexual pleasure, and interest in sex (Opbroek *et al*., 2002). However, Balon (2002) criticised this study for using a clinical measure of apathy without validity, and for not specifying which aspects of the broad term 'sexual functioning' were impaired in patients. Moreover, he stressed that some 'emotional blunting' manifestations could be personality traits or residual MDD symptoms. The issue of whether apathy symptoms are medication-induced or residual symptoms of MDD is a frequent puzzle (e.g. Fava *et al*., 2006; 31, 42).

A cross-sectional study explored side effects of long-term pharmacotherapy with antidepressants in 117 MDD patients who had initially responded to a 3-month acute treatment (Fava *et al*., 2006): a study-specific questionnaire was used to inquire for apathy, among other side effects. Up to 30–40% of the patients reported apathy and loss of motivation. The authors concluded that apathy is frequent in long-term pharmacotherapy of MDD and may be due both to medication and residual psychopathology.

A retrospective case–control study – using a 20-year database – investigated the specificity of SSRIs to cause emotional blunting in antidepressant-treated elderly inpatients ($N = 384$) with MDD and/or dysthymia (Wongpakaran *et al*., 2007). A study-specific clinical measure of apathy – combining items from established depression rating scales – was used. At discharge, depressive symptomatology was significantly reduced, irrespective of the type of antidepressant prescribed. However, SSRI-treated patients demonstrated significantly greater apathy. Both the age range 70–75 years and the length of hospital stay predicted post-treatment apathy.

A qualitative study explored the phenomenology of SSRI-induced apathy in 38 SSRI-treated depressed or anxious patients, through interviews and inquiry of relevant posts in patient-oriented websites (Price *et al*., 2009). Findings suggested that SSRI administration is associated with 'emotional detachment' ranging from 'just not caring' for stimuli eliciting anxiety prior to treatment to generalised emotional numbing. More precisely, eight key framework 'themes' were identified, including 'general effects on all emotions', 'reduction of positive or negative emotions', 'emotional detachment', 'just-not-caring' manifestations, fears of 'changed personality', 'effects on everyday life (helpful and unhelpful)' and 'it's because of my pills!' statements, in which patients attributed their apathy symptoms to SSRI treatment. Notably, apathy manifestations were considered as *beneficial* by an unspecified proportion of patients, but others considered them as the cause of their financial and working problems.

A multicentre, double-blind, randomised study found that in 423 SSRI-treated patients with MDD in remission, but with clinically significant apathy, switching to the SNRI duloxetine was similarly effective to switching to another SSRI (escitalopram) regarding the reduction in apathy (Raskin *et al*., 2012). The authors suggest that the serotoninergic component of duloxetine may reduce its efficacy to alleviate apathy symptomatology and that a 'pure' noradrenergic drug might prove more effective. Of note, another 60 patients who had been receiving escitalopram already at baseline, and continued this medication for a further 8 weeks, also demonstrated an improvement in apathy. Data from this study were additionally used to assess the underlying structure of the RSAT and the Massachusetts General Hospital CPFQ for measuring apathy (Rothschild, 2008; Fava *et al*., 2009).

The clinical efficacy, safety, and tolerability of agomelatine have been confirmed (Pompili *et al*., 2013). A randomised, controlled, double-blind 24-week trial suggests that 'emotional blunting'" is less frequent with agomelatine (25–50 mg/day) than with escitalopram (10–20 mg/day), although the drugs had similar efficacy in treating MDD (Corruble *et al*., 2013). Apathy manifestations included lack of emotions' intensity (agomelatine = 28% vs. escitalopram = 60%) and lack of care for issues previously considered as important (agomelatine 16% vs. escitalopram 53%). The authors

https://doi.org/10.1017/neu.2023.6 Published online by Cambridge University Press

suggest that emotional blunting may not be a side effect of antidepressants, but a symptom of MDD that conventional clinical measures fail to trace and where agomelatine is superior to escitalopram. They also propose that the OQESA – used to evaluate apathy in the study – should be considered a clinical measure of MDD.

In another study, up to 22.6% of MDD patients and 18.2% of patients with an anxiety disorder demonstrated apathy manifestations after at least 6 months of successful SSRI monotherapy (Popovic *et al*., 2015). The overall incidence of apathy in the sample ($N = 67$) was 20.4%. The authors attribute the higher incidence of SSRI-induced apathy to the 'real-world setting', in contrast to the more rarefied environment of clinical trials, and hypothesised that partial responders, receiving combined pharmacotherapy, will have a higher incidence of apathy.

In another study, 57 depressed patients treated with serotoninergic antidepressants reported significantly greater subjective difficulty in identifying feelings, when compared to 441 controls (Kajanoja *et al*., 2018). A 16-week prospective study investigated various adverse effects of antidepressants in 98 MDD patients and found that as depressive symptoms (rated by the Montgomery-Asberg Depression Rating Scale, MADRS) gradually improved, apathy symptoms (OQESA) decreased (Ascibasi *et al*., 2020): furthermore, at Week 8 and Week 16, patients in remission demonstrated significantly lower apathy manifestations compared to non-remitted patients. The OQESA and the MADRS scores were significantly correlated in all assessments, suggesting that severity of apathy may be related to both the medication and the intensity of depressive symptoms.

A retrospective chart review of 119 outpatients with MDD or other diagnoses found that clinically important apathy emerged significantly more often and was more severe in SSRI-treated patients when compared to those treated with a non-SSRI antidepressant (92% vs. 61%) (Padala *et al*., 2020). Antidepressant-induced apathy was observed in all psychiatric disorders, especially in patients with dementia, and with all the SSRIs administered (citalopram, escitalopram, paroxetine, fluoxetine, sertraline).

### *Case reports*

Hoehn-Saric *et al* (1990) were the first to report the presence of apathy, indifference, loss of initiative, or disinhibition (without concurrent sedation or hypomania) in three MDD patients receiving 20 mg/day fluoxetine and two patients with panic disorder receiving fluvoxamine 300 mg/day and 400 mg/day, respectively. Clinical manifestations were dose-related and completely resolved ($N = 4$) or improved after dose reduction ($n = 1$), or after switching to another class of antidepressants. Remission of apathy took longer to achieve in fluoxetine-treated patients, possibly due to its longer half-life when compared to that of fluvoxamine.

A 23-year-old patient treated with high doses of fluoxetine (100 mg/day) for obsessive-compulsive disorder (OCD) demonstrated apathy, indifference, inattention, and perseveration and found to be associated with a decrease in cerebral blood flow in the frontal lobes and changes in neuropsychological measures suggesting frontal lobe impairment (Hoehn-Saric *et al*., 1991). Apathy completely resolved 4 weeks after discontinuing fluoxetine, concurrently with normalisation of cerebral blood flow and neuropsychological measurements. Likewise, an OCD patient with comorbid Tourette syndrome demonstrated a clinically significant 'frontal lobe syndrome' characterised mainly by apathy and indifference after a 4-week fluvoxamine (150 mg/day) treatment (George & Trimble, 1992), this syndrome resolving after dose reduction.

A 17-year-old female with MDD experienced fluoxetine (30 mg/day)-induced apathy which improved after dose reduction (to 20 mg/day) and augmentation with bupropion (150 mg/day) (Garland & Baerg, 2001). Sertraline-induced apathy was described in a 48-year-old male with MDD and 'personality change due to medical condition', which resolved after dosage reduction (Kodela & Venkata, 2010). Likewise, the panic symptoms of a 39-year-old female improved with sertraline (50 mg/day), but she also demonstrated flattening of emotions and a 'like-nothing-matters' feeling: these apathy manifestations abated after dosage reduction to 25 mg/day (Sato & Asada, 2011).

In another report, among six patients demonstrating SSRI-induced loss of motivation, four improved only by discontinuing medication, and two resolved after switching to a dopaminergic agent (bupropion) (Padala *et al*., 2012). In another report, a 70-year-old male MDD patient improved moderately after 6 months of escitalopram treatment (10 mg/day), but later demonstrated apathy manifestations, including loss of drive and motivation, without however worsening of depression (De Berardis *et al*., 2013): co-administration of agomelatine (25 mg/day) for 9 weeks both reversed the escitalopram-induced apathy and preserved the therapeutic gains of the latter, which subsequently was discontinued.

In another report, a 42-year-old male patient with depression and epilepsy received a carbamazepine–topiramate–sertraline combination, which reduced depression and terminated seizures: however, he demonstrated apathy which did not remit after carbamazepine cessation, but only after administration of amisulpride (15 mg/day) (Monga & Padala, 2015). The case of a 67-year-old female MDD patient was reported, who while receiving combined fluoxetine–venlafaxine–mirtazapine–aripiprazole pharmacotherapy experienced severe symptoms of apathy which abated after discontinuation of all antidepressants and co-administration of methylphenidate (25 mg/day)-modafinil (200 mg/day)-olanzapine (10 mg/day) (Kim *et al*., 2019).

Additionally, two male MDD patients receiving venlafaxine (75 and 37.5 mg/day, respectively) experienced mild apathy symptoms which abated after increasing the dosage to 150 mg/day (Sato *et al*., 2020). The authors consider the serotoninergic mechanisms that prevail with low doses of venlafaxine to cause apathy, which subsequently abates with dosage increases which result in a better serotonin/norepinephrine balance.

### *Internet/telephone surveys and investigation of patient-oriented websites*

In a telephone survey (semi-structured interview) of 161 MDD patients who had completed SSRI therapy, up to 20% reported 'apathy', while 16.1% suffered from loss of ambition (Bolling & Kohlenberg, 2004). Another study explored reviews in three popular health Internet-websites concerning the antidepressants escitalopram, duloxetine, vilazodone, and vortioxetine (Hughes *et al*., 2017): participants ($N = 3243$) reported suffering from anxiety, depressive, or bipolar disorders. Patients receiving vilazodone or vortioxetine more often reported 'emotional instability'. 'Emotional numbing' was more often reported by patients on escitalopram (10.7%) or duloxetine (8.2%), compared to those on vortioxetine (5.9%) or vilazodone (4.1%): overall, 9.4% of subjects reported 'emotional blunting'.

The adverse effects reported by 258 patients receiving antidepressants (SSRIs, TCAs, 'other') were compared to those reported by clinicians, through an internet-based medicine reporting system (van Geffen *et al*., 2007). Up to 10.8% of patients reported 'apathy', while none of the clinicians reported apathy

https://doi.org/10.1017/neu.2023.6 Published online by Cambridge University Press

in their antidepressant-treated patients. Up to 46% of the patients who reported apathy perceived it as 'very negative', and up to 54% discontinued pharmacotherapy.

In a patient-oriented website, the views of 468 subjects receiving venlafaxine or fluoxetine were explored (Goldsmith & Moncrieff, 2011). Apathy manifestations ('flat mood', 'unable to cry very often', 'numb', 'blank', 'no motivation', 'lack of interest', 'distanced from life', 'loss of humour', 'less creative', 'less motivated', 'it seems less me', etc.) were reported by 17% and 19% of responders to venlafaxine and fluoxetine, respectively. Apathy was associated with cognitive impairment, reduced libido, and sedation. The authors suggested that antidepressant-induced reduced libido is not an isolated effect but related to emotional blunting caused by these medications. Moreover, feelings of emotional blunting or indifference coexisted with activation/arousal effects and emotional instability and – most importantly – with suicidal thoughts. The researchers suggest that emotional blunting reduces normal inhibitions, which in turn results in the emergence of suicidal ideation (Goldsmith & Moncrieff, 2011).

An internet-based survey investigated the rate of antidepressant-induced emotional blunting in 669 currently depressed patients under *monotherapy* with either an SSRI (citalopram, escitalopram, fluoxetine, paroxetine, or sertraline) or a non-SSRI-antidepressant (amitriptyline, bupropion, desvenlafaxine, duloxetine, mirtazapine, or venlafaxine) and 150 drug-free, previously depressed controls (Goodwin *et al*., 2017). Overall, the rate of emotional blunting in currently depressed patients was 46% (men vs. women = 52% vs. 44%). Contrary to the notion that apathy is seen only in SSRI-treated patients, the authors found no major differences between agents in apathy emergence, although it appeared less evident with bupropion. Currently, depressed patients had significantly higher emotional blunting scores on the OQESA compared to controls, while total blunting score was correlated with depression severity. Of those reporting emotional blunting, 37% had a negative perception of the condition, but up to 38% had a positive perception. In summary, this study suggests that almost half of MDD patients receiving antidepressants demonstrate emotional blunting. Moreover, it suggests that emotional blunting is not merely a side effect of antidepressants but also a symptom of depression and associated with a poorer outcome.

An internet-based survey designed to elicit experiences with antidepressants (SSRIs, TCAs, and venlafaxine), of 1829 adults who had started pharmacotherapy in the preceding 5 years (52% were treated for >3 years) (Read *et al*., 2014; Cartwright *et al*., 2016), found a high prevalence of apathy symptoms, including 'feeling emotionally numb' (60%), 'reduction in positive feelings' (42%), and 'caring less about others' (39%): all apathy manifestations were reported as being associated with 'suicidality'.

Another online survey, in 38 countries, asked 1431 users of antidepressants for the presence and severity of symptoms 'as a result of taking the antidepressant' (Read & Williams, 2018). Apathy manifestations included 'feeling emotionally numb' (71%; the most frequently reported adverse effect), 'reduction in positive feelings' (60%), and 'caring less about others' (54.5%). Less than 5% of patients reported being informed prior to pharmacotherapy about the potential emergence of medication-induced apathy. The authors conclude that asking people directly reveals far higher rates of medication-induced manifestations than clinicians consider, including apathy. In another online survey, 342 users of antidepressants were asked open questions concerning their pharmacotherapy (e.g. 'Is there anything else you would like to tell us about your experience of taking medication?'): up to 5.8% reported that their feelings were blunted by the antidepressant, using terms like 'flattened' or 'numbed' (Read *et al*., 2020).

Camino *et al* (2022) recently analysed 450 posts from a patient-oriented website – 50 on each of the most prescribed antidepressants, including bupropion, citalopram, duloxetine, escitalopram, fluoxetine, mirtazapine, paroxetine, sertraline, and venlafaxine. Sertraline, paroxetine, and fluoxetine were associated with frequent reports of emotional blunting, but bupropion with very few. The presence of emotional blunting was among the side effects (the other being suicidality, irritability, cognitive disturbances, and withdrawal symptoms) that were inversely associated with satisfaction with antidepressant treatment. After adjusting for confounders, only emotional blunting was more frequently reported by users of serotoninergic agents, as compared to non-serotoninergic agents. The authors concluded that patients/users may prefer receiving a non-serotonergic agent over a serotonergic one, due to the lower propensity of the former to induce emotional blunting.

Recently, Christensen *et al* (2022) reported data from an internet-based survey of 752 MDD patients (female = 62%) in acute ($N = 300$) or remission phase, currently receiving a prescribed antidepressant, who reported emotional blunting during the last 6 weeks. Emotional blunting was assessed using the Oxford Depression Questionnaire. Antidepressant agents taken by patients included agomelatine, bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, mirtazapine, paroxetine, sertraline, venlafaxine, and vortioxetine. Up to 44% of patients rated their emotional blunting as 'extremely severe'. Up to 45% of study patients believed that antidepressant medication was the cause of their emotional blunting: as a result, one-third of patients were either considering stopping or had stopped the medication.

### *Studies in children and adolescents*

Previous data have also suggested the presence of SSRI-induced apathy in paediatric populations (Garland & Baerg, 2001; Reinblatt & Riddle, 2006). Its prevalence in children treated for anxiety disorders was reported to be 5% (Reinblatt & Riddle, 2006). Garland and Baerg (2001) were the first to report five 'typical cases' (2 OCD, 2 depressed and one anxious) of SSRI (fluoxetine, paroxetine)-induced apathy and lack of motivation – one accompanied by disinhibition – in a 10-year-old child and in four adolescents (14–17 years old). Symptoms were dose-related and reversible after dosage reduction without ($N = 4$) or with bupropion (150 mg/day) co-administration. The authors stress that the delayed onset, subtlety of symptoms, lack of subjective awareness, and the resulting disability indicate a need for clinicians to inform families for the possible emergence of apathy when children/adolescents are prescribed SSRIs. Another study reported that among 45 non-depressed paediatric patients with anxiety disorders who received fluvoxamine, two patients (5%) demonstrated apathy (Reinblatt & Riddle, 2006): both presentations were characterised by lack of awareness, delayed onset, dose-dependency, and reversibility following reduction of dosage or discontinuation.

### *Reduction of crying and other emotional symptoms without emergence of apathy in SSRI-treated subjects*

Previous data suggest that some MDD patients and healthy volunteers with emotional lability demonstrate SSRI-induced reduction of crying, but without suffering from concurrent apathy. Rapid improvement of excessive or inappropriate crying without

https://doi.org/10.1017/neu.2023.6 Published online by Cambridge University Press

concurrent apathy was initially reported in SSRI-treated depressed patients (Oleshansky & Labbate, 1996). Subsequently, in a randomised, placebo-controlled trial, a single dose (20 mg) of paroxetine significantly inhibited the crying behaviour of 25 healthy, young females in response to emotional movies, without concurrent mood changes (van der Veen *et al.*, 2012).

Eight female MDD patients reported that after SSRI therapy they ceased to cry during moving film scenes, although their overall emotional experience was left intact (Vinar, 2000). Another case study explored the effect of SSRIs on 'emotional lability', that is, poor control of emotions manifested as tearfulness, weeping, and crying spells (Scoppetta *et al.*, 2005): participants (3 MDD patients, 2 controls) received an SSRI for 5-day cycles and all reported total remission of emotional lability after a few days of pharmacotherapy. In another case report, all seven SSRI-treated patients demonstrated inability to cry soon after starting pharmacotherapy, although feelings of sadness and the urge to cry remained intact (Holguin-Lew & Bell, 2013). The different secondary pharmacological effects of the various SSRIs administered (fluvoxamine on sigma-1 receptors, sertraline on dopamine receptors, and citalopram and escitalopram on histamine receptors) led the authors to suggest that the amelioration of crying behaviour was probably due to their common serotoninergic effect.

### *Clinical conditions in which SSRIs might improve apathy*

Some data suggest that SSRIs may improve apathy in patients with dementia. However, other reports do not support this notion (Azhar *et al.*, 2022). Thus, in non-depressed behaviourally disturbed patients with Alzheimer's disease, administration of citalopram was associated with up to 60% reduction in scores of the Apathy subscale of the Neuropsychiatric Inventory (Siddique *et al.*, 2009). Likewise, in a mix of patients with Alzheimer's disease or vascular dementia, Nyth and Gottfries (1990) reported a significant reduction in apathy in the citalopram group in at week 4 in comparison with baseline. However, this reduction in apathy was not significant when compared with placebo. Another study in patients with the same diagnoses as in the previous study did not show any effect of citalopram in apathy (Pollock *et al.*, 2002).

### *Other medications that may induce apathy symptoms*

Apathy manifestations may emerge as a consequence of treatment with antipsychotics. More precisely, antipsychotic medications – both typical and atypical – may induce a condition known as neuroleptic-induced deficit syndrome (NIDS) which includes apathy, lack of initiative, anhedonia, indifference, blunted affect, and reduced insight into disease. The concept of NIDS is well described in patients with schizophrenia. However, antipsychotics are widely used in patients with depressive or bipolar disorders. Thus, antipsychotics can make depression or bipolar disorder resemble other more refractory conditions and may lead clinicians to mistaken diagnoses and inappropriate treatments (Szmulewicz *et al.*, 2016). Such cases have been already described in literature (Ueda *et al.*, 2016). Moreover, it has been proposed that antipsychotic drugs do not extinguish psychotic symptoms, but rather they produce emotional detachment due to down-regulation of dopamine turn-over (Kapur, 2003). It also assumes that apathy and lack of initiative is an unwanted consequence of the same psychological mechanism that relieves psychotic symptoms (Kapur *et al.*, 2006).

Data from healthy subjects and case reports suggest that lithium can induce an amotivational syndrome in healthy volunteers (e.g. Kropf & Muller-Oerlinghausen, 1979) or in patients with bipolar disorders (e.g. Folstein *et al.*, 1982). This follows a dose-response pattern being more prominent in patients with higher lithium serum levels (Szmulewicz *et al.*, 2016). Regarding anticonvulsant medications, as already mentioned, a case report suggests that carbamazepine-topiramate combination administered for epilepsy together with sertraline for depression was associated with emergence of significant apathy (Monga & Padala, 2015).

## Discussion

To summarise, in patients with depressive, anxiety or other psychiatric disorders, pharmacotherapy with antidepressants (mostly with SSRIs, but in some cases with antidepressants from other classes) may induce an array of clinically significant manifestations, collectively termed "*apathy syndrome*" or "*emotional blunting*". These manifestations – which often have an insidious onset – include lack of motivation or dullness and, more generally, a decrease in emotional responsiveness to numerous circumstances which would have triggered intense mood reactions prior to antidepressant pharmacotherapy. The prevalence of apathy syndrome in patients receiving either an SSRI or a non-SSRI antidepressant ranges from 5.8% to almost 50% in the related reports. However, the prevalence of apathy manifestations in samples treated only with SSRIs ranges between 20% and 92%. A number of researchers assume that apathy symptoms, at least in depressive patients, may be attributed to both the antidepressant medication and to the clinical syndrome. Other researchers have suggested that emotional blunting may not be a side effect of antidepressants, but solely a symptom of depression which is not traced by conventional clinical measures.

Antidepressant-induced apathy emerges independently of the psychiatric disorder for which the drug is prescribed and can be found in all age-groups. Furthermore, it is independent of treatment outcome and may be clinically present even after depressive or other psychopathology has remitted. Libido reduction may be a sexual accompaniment of antidepressant-induced apathy syndrome, while some clinicians consider violent behaviours in adolescents to be related, at least partly, to antidepressants-induced apathy. Often, apathy symptoms are not raised by the patient and/or relatives and so remain untreated, with subsequent clinical, social, and professional consequences.

Clinicians should be alert for antidepressant-induced apathy when there is clinically prominent loss of motivation, especially since this syndrome is dose-dependent and reversible. If the clinician is not sure whether emotional blunting is a side effect of the antidepressant or a residual symptom of MDD, it has been recommended firstly to increase the dose. If the symptoms are due to apathy and not to MDD, they are expected to worsen, in which case the clinician can safely reduce the drug's dosage. Therefore, the clinician avoids a potential relapse of MDD, if he initially reduces the antidepressant's dose mistakenly assuming it is apathy syndrome: but this is an approach with some drawbacks. Few data exist as to the pharmacotherapy of the antidepressant-induced apathy syndrome and are limited to case reports describing treatment with bupropion, agomelatine, or amisulpride and an open-label study of olanzapine administration.

The main limitation of this review is the paucity of clinical trials – especially randomised placebo-controlled ones – as most 'studies' are either case reports or internet/telephone surveys in samples of "users" of antidepressant medications. Furthermore, in many of these reports, non-specific clinical measures – or no measures at all – are used to evaluate apathy symptoms. The retrospective

https://doi.org/10.1017/neu.2023.6 Published online by Cambridge University Press

nature of many reports cannot exclude the possibility that patients were treated with SSRIs rather than with other antidepressants because of accompanying factors which may also have influenced apathy. Therefore, placebo-controlled clinical trials with larger patient samples, using more sophisticated clinical measures are needed in order to overcome these limitations and to permit more reliable inferences about a number of critical issues concerning the antidepressant-induced apathy syndrome: including its prevalence, nature and course (e.g. whether it is an adverse effect of the drug, a residual symptom of the disease, or a combination of both), biological underpinnings, predisposing factors, and treatment strategies.

**Acknowledgements.** None.

**Financial support.** None.

**Conflict of interest.** DSB is current (2022-24) President of the British Association for Psychopharmacology, former Chair of the Psychopharmacology Committee of the Royal College of Psychiatrists (2017-20), a current Medical Patron of Anxiety UK, and has researched, prescribed and taken antidepressant drugs.

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