**APATHY ASSOCIATED WITH ANTIDEPRESSANT DRUGS – A SYSTEMATIC REVIEW**

**Vasilios G. Masdrakis\*, Manolis Markianos\*, David S. Baldwin\*\* ¶**

**\*National and Kapodistrian University of Athens, School of Medicine,**

**First Department of Psychiatry, Eginition Hospital**

**74 Vas. Sofias Avenue, 11528 Athens, Greece**

**\*\*University Department of Psychiatry, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, United Kingdom**

Running Title: Antidepressant-induced Apathy

**¶ Corresponding author:** David S. Baldwin MA DM FRCPsych, University Department of Psychiatry, Academic Centre, College Keep, 4-12 Terminus Terrace, Southampton SO14 3DT; Tel. + 44 02382 310 764; Fax + 44 02382 310 766. E-mail address: D.S.Baldwin@soton.ac.uk

**Conflicts of Interest and Source of Funding:** None to declare.

**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%-50%, and for SSRIs ranges between 20%-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, etiology, and treatment of this important clinical condition.

**Keywords:** antidepressant drugs; apathy syndrome; emotional blunting; selective serotonin reuptake inhibitors.

**SUMMATIONS**

* Pharmacotherapy with antidepressants (mostly SSRIs) may induce an array of clinically significant manifestations, collectively termed “apathy syndrome” or “emotional blunting”. Its prevalence ranges from 5.8% to almost 50%, but in samples treated only with SSRIs ranges 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.
* If the clinician is not sure whether emotional blunting is a side effect of the antidepressant or a residual symptom of depression, it is recommended firstly to increase the dose. If the symptoms are due to apathy and not to depression, they are expected to worsen, in which case the clinician can safely reduce the drug’s dosage.

**CONSIDERATIONS**

* There is a paucity of clinical trials, especially randomized 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 treated with SSRIs rather than with other antidepressants because of accompanying factors which may also have influenced apathy.

**1. INTRODUCTION**

In patients with depressive, anxiety or other psychiatric disorders, pharmacotherapy with antidepressants (mostly 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 narrower term “*inability to cry*”) (e.g. Hoehn-Saric et al., 1990; Hoehn-Saric et al., 1991; George and Trimble, 1992; Garland and Baerg, 2001; Barnhard 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 and Sansone, 2010; Lee and 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.

**2. METHOD FOR THE LITERATURE REVIEW**

**2.1. 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 used to decide whether to include a report in our review.

*2.1.1. Inclusion criteria*

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

*2.1.2. Exclusion criteria*

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

**2.2. Search methodology**

In the PUBMED search, we combined the terms “apathy” (sub-section 2.2.1.), “crying” (2.2.2.) and “emotional blunting” (2.2.3.) with various terms concerning classes of antidepressant medications e.g. “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.

*2.2.1. 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=**20**); [2] “apathy + SSRIs” (N=83, E=**2**); [3] “apathy syndrome + selective serotonin reuptake inhibitors” (N=29, E=**3**); [4] “apathy syndrome + SSRIs” (N=24, E=0); [5] “apathy + serotonin noradrenaline reuptake inhibitors’ (N=11, E=**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=**4**); [14] ‘apathy syndrome + ‘antidepressants’ (N=63. E=**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 R, et al., 1991; George and Trimble, 1992; Garland and Baerg 2001; Barnhart et al., 2004; Padala et al., 2020; Kelly et al., 2008; Sansone and Sansone, 2010; Lee and 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 and Riddle, 2006; Kodela and Venkata, 2010; De Berardis et al., 2013; Kim et al., 2019; Marangell et al., 2002; Bolling and Kohlenberg, 2004; Settle, 1998; Cassano and Fava, 2004; van Geffen et al., 2007; Wongpakaran et al., 2007; Sato and 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 and 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 and Sansone, 2010; Lee and Keltner, 2005).

*2.2.2. 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=**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)΄[7] “crying + antidepressants” (N=144, E=**1**).

Consequently, the total number of papers that were deemed eligible to be included in the present review was **6** (Scoppetta et al., 2005; Opbroek et al., 2002; Oleshansky et al., 1996; Vinar, 2000; van der Veen et al., 2012; Holguin-Lew and Bell, 2013).

*2.2.3. 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=**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); [7] “emotional blunting + antidepressants” (N=107, E=**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 and Moncrieff, 2011; Balon, 2002; Corruble et al., 2013; Cartwright et al., 2016; Hughes et al., 2017; Kajanoja et al., 2018; Read and 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 paperconcerning adverse effects – including emotional blunting - of SSRIs only (Marazziti et al., 2019).

**3. 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 subsection-2.2.). 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 3.1.), in its etiology and treatment (3.2.), while in the final sub-section (3.3.) we refer in more detail to data from previous relevant reports.

3.1. Antidepressant-induced apathy syndrome: definition, clinical features, differential diagnosis, and prevalence

*3.1.1. 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 and Trimble, 1992; Garland and 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 “attenuate” or “set aside everyday concerns” (Kelly et al., 2008; Sansone and 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 and 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 others 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, one 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-3.3.

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

*3.1.2. 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 and 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) emphasize that this relationship depends on how apathy is conceptualized. 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 (AES) (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 (OQuESA) (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 and Wilkosz, 2005).

*3.1.3. 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 pediatric populations, 5% of 45 patients with anxiety disorders receiving the SSRI fluvoxamine demonstrated apathy symptomatology, without concomitant depression (Reinblatt and Riddle, 2006). More data about the prevalence of antidepressant-induced apathy are mentioned in subsection-3.3.

3.2. Etiology and treatment

*3.2.1. Etiology*

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 is 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 behavior (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: i.e. 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 and Keltner 2005; Szmulewicz et al., 2016; Levy and 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-centered” mechanism, altering a patient’s mental state which subsequently impacts MDD psychopathology, rather than through a “disease-centered” way, i.e. 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.

*3.2.2. Treatment*

3.2.2.1. 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 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 and 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 and 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 evidence for this approach is very limited.

3.2.2.2. Pharmacotherapy of antidepressants-induced apathy

Relevant data are limited to cases treated with bupropion (Garland and Baerg, 2001), agomelatine (De Berardis et al., 2013), amisulpride (Monga and 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 subsection-3.3. and **TABLE**).

3.2.2.3. Considering antidepressants-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 and Kohlenberg, 2004;Price et al., 2009;Goldsmith and 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 and Keltner 2005; Price et al., 2009;Moncrieff, 2015).

3.3. Clinical trials, case-reports, and internet/telephone surveys

In each of the following sub-sections (3.3.1.-3.3.3.), studies are reviewed in chronological order: for reports from the same year, alphabetical order is followed.

*3.3.1. 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/d). 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) criticized 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 generalized 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 multicenter, double-blind, randomized 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 Rothschild Scale for Antidepressant Tachyphylaxis (RSAT) and the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) for measuring apathy (Rothschild, 2008;Fava et al., 2009).

The clinical efficacy, safety, and tolerability of agomelatine has been confirmed (Pompili et al., 2013). A randomized, controlled, double-blind 24-week trial suggests that “emotional blunting” is less frequent with agomelatine (25-50 mg/d) than with escitalopram (10-20 mg/d), 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 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 Oxford Questionnaire on the Emotional Side-effects of Antidepressants (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 six 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 rarified environment of clinical trials; and hypothesized 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 both to 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).

*3.3.2. 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/d fluoxetine and two patients with panic disorder receiving fluvoxamine 300 mg/d and 400 mg/d 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, 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 four weeks after discontinuing fluoxetine, concurrently with normalization of cerebral blood flow and neuropsychological measurements. Likewise, an OCD patient with comorbid Tourette syndrome demonstrated a clinically significant “frontal lobe syndrome” characterized mainly by apathy and indifference after a 4-week fluvoxamine (150 mg/d) treatment (George and Trimble, 1992), this syndrome resolving after dose reduction.

A 17-year-old female with MDD experienced fluoxetine (30 mg/d)-induced apathy which improved after dose reduction (to 20 mg/d) and augmentation with bupropion (150 mg/d) (Garland and 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 and Venkata, 2010).Likewise, the panic symptoms of a 39-year-old female improved with sertraline (50 mg/d), 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 and 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 six months of escitalopram treatment (10 mg/d), but later demonstrated apathy manifestations, including loss of drive and motivation, without however worsening of depression (De Berardis et al., 2013): coadministration of agomelatine (25 mg/d) 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/d) (Monga and 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/d)-modafinil (200 mg/d)-olanzapine (10 mg/d) (Kim et al., 2019).

Additionally, two male MDD patients receiving venlafaxine (75 and 37.5 mg/d respectively) experienced mild apathy symptoms which abated after increasing the dosage to 150 mg/d (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.

*3.3.3. 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 and 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 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 and Moncrieff, 2011). Apathy manifestations (“flat mood”, “unable to cry very often”, “numb”, “blank”, “no motivation”, “lack of interest”, “distanced from life”, “loss of humor”, “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 and Moncrieff, 2011).

An internet-based survey investigated the rate of antidepressant-induced emotional blunting in 669 currently depressed patients under *monotherapy* with either a 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 to 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 five years (52% were treated for >3years) (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 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 and 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 analyzed 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.

*3.3.4. Studies in children and adolescents*

Previous data have also suggested the presence of SSRI-induced apathy in pediatric populations (Garland and Baerg; 2001; Reinblatt and Riddle, 2006). Its prevalence in children treated for anxiety disorders was reported to be 5% (Reinblatt and 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/d) 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 pediatric patients with anxiety disorders who received fluvoxamine, two patients (5%) demonstrated apathy (Reinblatt and Riddle, 2006): both presentations were characterized by lack of awareness, delayed onset, dose-dependency, and reversibility following reduction of dosage or discontinuation.

*3.3.5. 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 concurrent apathy was initially reported in SSRI-treated depressed patients (Oleshansky and Labbate, 1996). Subsequently, in a randomized, placebo-controlled trial, a single dose (20 mg) of paroxetine significantly inhibited the crying behavior 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”, i.e. poor control of emotions manifested as tearfulness, weeping, and crying spells (Scoppetta et al., 2005): participants (3 MDD patients, 2 controls) received a 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 and 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 behavior was probably due to their common serotoninergic effect.

3.3.6 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 behaviorally disturbed patients with Alzheimer 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).

3.3.7. 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 schizophrenia. However, nowadays antipsychotics are widely used in depressive and 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 et al., 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 and 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 and Padala, 2015).

**4. DISCUSSION**

To summarize, 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 a 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 behaviors 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 randomized 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 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.

**REFERENCES**

**Arnone D, Horder J, Cowen PJ, Harmer CJ** (2009) Early effects of mirtazapine on emotional processing. *Psychopharmacology (Berl)* **203**, 685-691.

**Ascibasi K, Cokmus FP, Dikici DS, Ozkan HM, Alci D, Altunsoy N, Kuru E, Yuzeren S, Aydemir O** (2020) Evaluation of emotional adverse effects of antidepressants. A follow-up study. *Journal of Clinical Psychopharmacology* **40**, 594-598.

**Azhar L, Kusumo RW, Marotta G, Lanctot KL, Herrmann N** (2022) Pharmacological management of apathy in dementia. *CNS Drugs* **36**, 143-165.

**Balon R** (2002) Emotional blunting, sexual dysfunction and SSRIs. International Journal of *Neuropsychopharmacology* **5**, 415-416.

**Barnhart J, Makela, EH, Latocha MJ** (2004) SSRI-induced apathy syndrome: a clinical review. *Journal of Psychiatric Practice* **10**, 196-199.

**Bolling MY, Kohlenberg RJ** (2004) Reasons for quitting serotonin reuptake inhibitor therapy: paradoxical psychological effects and patient satisfaction. *Psychotherapy and Psychosomatics* **73**, 380-385.

**Camino S, Strejilevich SA, Godoy A, Smith J, Szmulewicz A** (2022) Are all antidepressants the same? The consumer has a point. *Psychological Medicine* *IN PRESS*; doi: <https://doi.org/10.1017/s0033291722000678>

**Cartwright C, Gibson K, Read J, Cowan O, Dehar T** (2016) Long-term antidepressant use: patient perspectives of benefits and adverse effects. *Patient Preference and Adherence* **10**, 1401-1407.

**Carvalho AF, Sharma MS, Brunoni AR, Vieta E, Fava GA** (2016) The safety, tolerability and risks associated with the use of newer generation antidepressant drugs: a critical review of the literature. *Psychotherapy and Psychosomatics* **85**, 270-288.

**Cassano P, Fava M** (2004) Tolerability issues during long-term treatment with antidepressants. *Annals of Clinical Psychiatry* **16**, 15-25.

**Christensen MC, Ren H, Fagiolini A** (2022) Emotional Blunting in patients with depression. Part I: clinical characteristics. *Annals of General Psychiatry* **21**, 10.

**Corruble E, de Bodinat C, Belaidi C, Goodwin GM and on behalf of the agomelatine study group** (2013) Efficacy of agomelatine and escitalopram on depression, subjective sleep and emotional experiences in patients with major depressive disorder: a 24-wk randomized, controlled, double-blind trial. *International Journal of Neuropsychopharmacology* **16**, 2219-2234.

**De Berardis D, Valchera A, Fornaro M, Serroni N, Marini S, Moschetta SM, Martinotti G, Di Giannantonio M** (2013) Agomelatine reversal of escitalopram-induced apathy: a case report. *Psychiatry and Clinical Neurosciences* **67**, 190-191.

**Fava M, Graves LM, Benazzi F, Scalia MJ, Josifescu DV, Alpert JE, Papakostas GI** (2006) A cross-sectional study of the prevalence of cognitive and physical symptoms during long-term antidepressant treatment. *Journal of Clinical Psychiatry* **67**, 1754-1759.

**Fava M, Iosifescu DV, Pedrelli P, Baer L** (2009) Reliability and validity of the Massachusetts general hospital cognitive and physical functioning questionnaire. *Psychotherapy and Psychosomatics* **78**, 91-97.

**Folstein MF, DePaulo JR, Trepp K** (1982) Unusual mood stability in patients taking lithium. *British Journal of Psychiatry* **140,** 188-191.

**Garland EJ, Baerg EA** (2001) Amotivational syndrome associated with selective serotonin reuptake inhibitors in children and adolescents. *Journal of Child and Adolescent Psychopharmacology* **11**, 181-186.

**George MS, Trimble MR** (1992) A fluvoxamine-induced frontal lobe syndrome in a patient with comorbid Gilles de la Tourette’s syndrome and obsessive-compulsive disorder. *Journal of Clinical Psychiatry* **53**, 379-380.

**Gobert A, Rivet JM, Lejeune F, Newman-Tancredi A, Adhumeau-Auclair A, Nicolas JP, Cistarelli L, Melon C, Millan MJ** (2002) Serotonin (2C) receptors tonically suppress the activity of mesocortical dopaminergic and adrenergic, but not serotonergic, pathways: a combined dialysis and electrophysiological analysis in the rat. *Synapse* **36**, 205-221.

**Goldsmith L, Moncrieff J** (2011) The psychoactive effects of antidepressants and their association with suicidality. *Current Drug Safety* **6**, 115-121.

**Goodwin GM, Price J, De Bodinat C, Laredo J** (2017) Emotional blunting with antidepressant treatments: a survey among depressed patients. *Journal of Affective Disorders* **221**, 31-35.

**Harmer CJ, Sheley NC, Cowen PJ, Goodwin GM** (2004) Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. *American Journal of Psychiatry* **161**, 1256-1263.

**Harmer CJ, de Bodinat C, Dawson GR, Dourish CT, Waldenmaier L, Adams S, Cowen PJ, Goodwin GM** (2011) Agomelatine facilitates positive versus negative affective processing in healthy volunteer models. *Journal of Psychopharmacology* **25**, 1159-1167.

**Hughes S, Lacasse J, Fuller RR, Spaulding-Givens J** (2017) Adverse effects and treatment satisfaction among online users of four antidepressants. *Psychiatry Research* **255**, 78-86.

**Hoehn-Saric R, Lipsey JR, McLeod DR** (1990) Apathy and indifference in patients on fluvoxamine and fluoxetine. *Journal of Clinical Psychopharmacology* **10**, 343-345.

**Hoehn-Saric R, Harris GJ, Pearlson GD, Cox CS, Machlin SR, Camargo EE** (1991) A fluoxetine-induced frontal lobe syndrome in an obsessive-compulsive patient. *Journal of Clinical Psychiatry* **52**, 131-133.

**Holguin-Lew JC, Bell V** (2013) “When I want to cry I can’t”: inability to cry following SSRI treatment. *Revista Colombiana de Psiquiatria* **42**, 304-310.

**Kapur S** (2003) Psychosis as a state of aberrant salience: a framework linking biology, phenomenology and pharmacology in schizophrenia. *American Journal of Psychiatry* **160,** 13-23.

**Kapur S, Agid O, Mizrahi R, Li M** (2006) How antipsychotics work – from receptors to reality. *NeuroRx* **3,** 10-21.

**Kajanoja J, Scheinin NM, Karukivi M, Karlsson, L, Karlsson H** (2018) Is antidepressant use associated with difficulty identifying feelings? A brief report. *Experimental and Clinical Psychopharmacology* **26**, 2-5.

**Kelly K, Posternak, M, Alpert JE** (2008) Toward achieving optimal response: understanding and managing antidepressant side effects. *Dialogues in Clinical Neuroscience* **10**, 409-418.

**Kim HG, Koo BH, Lee SW, Cheon EJ** (2019) Apathy syndrome in a patient previously treated with selective serotonin reuptake inhibitors for depression. *Yeungnam University Journal of Medicine* **36**, 249-253.

**Kodela S, Venkata PD** (2010) Antidepressant induced apathy responsive to dose reduction. *Psychopharmacology Bulletin* **43**, 76-79.

**Kropf D, Muller-Oerlinghausen B** (1979) Changes in learning, memory, and mood duing lithium treatment. Approach to a research strategy. *Acta Psychiatrica Scandinavica* **59,** 97-124.

**Landes AM, Sperry SD, Strauss ME, Geldmacher DS** (2001) Apathy in Alzheimer’s disease. *Journal of the American Geriatrics Society* **49**, 1700-1707.

**Lee SI, Keltner NL** (2005) Antidepressant apathy syndrome. *Perspectives in Psychiatric Care* **41**, 188-192.

**Levy ML, Cummings JL, Fairbanks LA, Masterman D, Miller BL, Craig AH, Paulsen JS, Litvan I** (1998) Apathy is not depression. *Journal of Neuropsychiatry and Clinical Neurosciences* **10**, 314-319.

**Levy R, Dubois B** (2006) Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cerebral Cortex* **16**, 916-928.

**Marangell LB, Johnson CR, Kertz B, Zboyan HA, Martinez JM** (2002) Olanzapine in the treatment of apathy in previously depressed participants maintained with selective serotonin reuptake inhibitors: an open-label, flexible-dose study. *Journal of Clinical Psychiatry* **63**, 391-395.

**Marazziti D, Mucci F, Tripodi B, Carbone MG, Muscarella A, Falaschi V, Baroni S** (2019) Emotional blunting, cognitive impairment, bone fractures and bleeding as possible side effects of long-term use of SSRIs. *Clinical Neuropsychiatry* **16**, 75-85.

**Marin RS, Biedrzycki RC, Firinciogullari S** (1991) Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Research* **38**, 143-162.

**Marin RS, Wilkosz PA** (2005) Disorders of diminished motivation. *Journal of Head Trauma Rehabilitation* **20,** 377-388.

**Markianos M, Evangelopoulos ME, Koutsis G, Sfagos C** (2001) Evidence for involvement of central noradrenergic activity in crying proneness. *Journal of Neuropsychiatry and Clinical Neurorosciences* **23**, 403-408.

**McCabe C, Mishor Z, Cowen PJ, Harmer CJ** (2010) Diminished neural processing of aversive and rewarding stimuli during selective serotonin reuptake inhibitor treatment. *Biological* *Psychiatry* **67,** 439-445.

**Moncrieff J, Cohen D** (2005) Rethinking models of psychotropic drug action. *Psychotherapy and Psychosomatics* **74**, 145-153.

**Moncrieff J, Cohen D** (2006) Do antidepressants cure or create abnormal brain states? *PLoS Medicine* **3**, e240.

**Moncrieff J** (2015) Antidepressants: misnamed and misrepresented. *World Psychiatry* **14**, 302-303.

**Monga V, Padala PR** (2015) Aripiprazole for treatment of apathy. *Innovations in Clinical Neuroscience* **12**, 33-36.

**Nyth AL, Gottfries CG** (1990) The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders. A Nordic multicenter study. *British Journal of Psychiatry* **157,** 894-901.

**Oleshansky MA, Labbate LA** (1996) Inability to cry during SRI treatment. *Journal of Clinical Psychiatry* **57**, 593.

**Opbroek A, Delgado PL, Laukes C, McGahuey C, Katsanis J, Moreno FA, Manber R** (2002) Emotional blunting associated with SSRI-induced sexual dysfunction. Do SSRIs inhibit emotional responses? *International Journal of Psychopharmacology* **5**, 147-151.

**Padala PR, Padala KP, Monga V, Ramirez DA, Sullivan DH** (2012) Reversal of SSRI-associated apathy syndrome by discontinuation of therapy. *Annals of Pharmacotherapy* **46**, e8.

**Padala PR, Padala KP, Majagi AS, Garner KK, Dennis RA, Sullivan DH** (2020) Selective serotonin reuptake inhibitors-associated apathy syndrome. *Medicine* **99**, 33.

**Pollock BG, Mulsant BH, Rosen J, Mazumdar S, Bharucha A, Marin R, Jacob NJ, Huber KA, Kastango KB, Chew ML** (2002) Comparison of citalopram, perphenazine, and placebo for the acute treatment of psychosis and behavioral disturbances in hospitalized, demented patients. *American Journal of Psychiatry* **159**, 460-465.

**Pompili M, Serafini G, Innamorati M, Venturini P, Fusar-Poli P, Sher L, Amore M, Girardi P** (2013) Agomelatine, a novel intriguing antidepressant option enhancing neuroplasticity: a critical review. *World Journal of Biological Psychiatry* **14**, 412-431.

**Popovic D, Vieta E, Fornaro M, Perugi G** (2015) Cognitive tolerability following successful long term treatment of major depression and anxiety disorders with SSRI antidepressants. *Journal of Affective Disorders* **173**, 211-215.

**Price J, Cole V, Goodwin GM** (2009) Emotional side-effects of selective serotonin reuptake inhibitors: qualitative study. *British Journal of Psychiatry* **195**, 211-217.

**Price J, Cole V, Doll H, Goodwin GM** (2012) The Oxford Questionnaire on the Emotional Side-effects of Antidepressants (OQuESA): Development, validity, reliability and sensitivity to change. *Journal of Affective Disorders* **140**, 66-74.

**Raskin J, George T, Granger RE, Hussain N, Weizhing Z, Marangell LB** (2012) Apathy in currently non-depressed patients treated with a SSRI for a major depressive episode: outcomes following randomized switch to either duloxetine or escitalopram. *Journal of Psychiatric Research* **46**, 667-674.

**Read J, Cartwright C, Gibson K** (2014) Adverse emotional and interpersonal effects reported by 1829 New Zealanders while taking antidepressants. *Psychiatry Research* **216**, 67-73.

**Read J, Williams J** (2018) Adverse effects of antidepressants reported by a large international cohort: emotional blunting, suicidality, and withdrawal effects. *Current Drug Safety* **13**, 176-186.

**Read J, Grigoriu M, Gee A, Diggle J, Butler H** (2020) The positive and negative experiences of 342 antidepressant users. *Community Mental Health Journal* **56**, 744-752.

**Reinblatt SP, Riddle MA** (2006) Selective serotonin reuptake inhibitor-induced apathy: a pediatric case series. *Journal of Child and Adolescent Psychopharmacology* **16**, 227-233.

**Rothschild AJ** (2008) The Rothschild Scale for Antidepressant Tachyphylaxis: reliability and validity. *Comprehensive Psychiatry* **49**, 508-513.

**Rothschild AJ, Raskin J, Wang SN, Marangell LB, Fava M** (2014) The relationship between change in apathy and changes in cognition and functional outcomes in currently non-depressed SSRI-treated patients with major depressive disorder. *Comprehensive Psychiatry* **55**, 1-10.

**Sansone RA, Sansone LA** (2010) SSRI-induced indifference. *Psychiatry (Edgemont)* **7**, 14-18.

**Sato S, Asada T** (2011) Sertraline-induced apathy syndrome. *Journal of Neuropsychiatry and Clinical Neurosciences* **23**, E19.

**Sato S, Sodeyama N, Matsuzaki A, Shiratori Y** (2020) Apathy symptoms induced by low-dose venlafaxine: two cases. *Neuropsychopharmacology Reports* **40**, 196-197.

**Scoppetta M, di Gennaro G, Scoppetta C** (2005) Selective serotonin reuptake inhibitors prevent emotional lability in healthy subjects. *European Review for Medical and Pharmacological Sciences* **9**, 343-348.

**Settle EC Jr** (1998) Antidepressant drugs: disturbing and potentially dangerous adverse effects. *Journal of Clinical Psychiatry* **59 (Suppl 16)**, 25-30; discussion: 40-42.

**Siddique H, Hynan LS, Weiner MF** (2009) Effect of a Serotonin Reuptake Inhibitor on irritability, apathy and psychotic symptoms in patients with Alzheimer’ disease. *Journal of Clinical Psychiatry* **70,** 915-918.

**Starkstein SE, Leentjens AFG** (2008) The nosological position of apathy in clinical practice. *Journal of Neurology, Neurosurgery and Psychiatry* **79,** 1088-1092.

**Szmulewicz A, Samane C, Caravotta P, Martino DJ, Igoa A, Hidalgo-Mazzei D, Colom F, Strejilevich SA** (2016) Behavioral and emotional adverse events of drugs frequently used in the treatment of bipolar disorders: clinical and theoretical implications. *International Journal of Bipolar Disorders* **4**, 6.

**Ueda S, Sakayori T, Omori A, Fukuta H, Kobayashi T, Ishizaka K, Saijo K, Okubo Y** (2016) Neuroleptic-induced deficit syndrome in bipolar disorder with psychosis. *Neuropsychiatric Disease and Treatment* **12,** 265-268.

**van der Veen FM, Jorritsma J, Krijger C, Vingerhoets AdJ** (2012) Paroxetine reduces crying in young women watching emotional movies. *Psychopharmacology* **220**, 303-308.

**van Geffen ECG, van der Wal SW, van Hulten R, de Groot MCH, Egberts ACG, Heerdink ER** (2007) Evaluation of patients’ experiences with antidepressants reported by means of a medicine reporting system. *European Journal of Clinical Pharmacoology* **63**, 1193-1199.

**Vinar O** (2000) Can antidepressants of the SSRI type change the normal personality type? *Ceska a Slovenska Psychiatrie* **96**, 200-202.

**Wongpakaran N, van Reekum R, Wongpakaran T, Clarke D** (2007) Selective serotonin reuptake inhibitor use associates with apathy among depressed elderly: a case-control study. *Annals of General Psychiatry* **6**, 7.

**Zhou Y, Yao X, Han W, Wang Y, Li Z, Li Y** (2022) Distinguishing apathy and depression in older adults with mild cognitive impairment using text, audio, and video based on multiclass classification and shapely additive explanations. *International Journal of Geriatric Psychiatry* **37,** *IN PRESS,* DOI: <https://doi.org/10.1002/gps.5827>