

# The Interface



## SSRI-INDUCED INDIFFERENCE

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This ongoing column is dedicated to the challenging clinical interface between psychiatry and primary care—two fields that are inexorably linked.

### ABSTRACT

In the existing literature, selective serotonin reuptake inhibitor exposure has been occasionally associated with both behavioral apathy and emotional blunting. While frequently described as separate entities, these two syndromes are mutually characterized by indifference and may be united under the single moniker, “selective

serotonin reuptake inhibitor-induced indifference.” Little is known about the epidemiology or etiology of selective serotonin reuptake inhibitor-induced indifference and few empirical studies have been undertaken. However, this syndrome may be under-recognized by both clinicians and patients (i.e., low insight, particularly among children and adolescents), and is

characterized by an insidious onset, dose-dependent effects (i.e., higher selective serotonin reuptake inhibitor doses are more likely to result in symptoms), and complete resolution of symptoms with the discontinuation of the offending drug. Treatment strategies may include a dose reduction of the offending selective serotonin reuptake inhibitor, augmentation with a second drug, and/or discontinuation of the selective serotonin reuptake inhibitor and subsequent treatment with a nonselective serotonin reuptake inhibitor antidepressant.

### KEY WORDS

Selective serotonin reuptake inhibitor (SSRI), indifference, apathy, emotional blunting, side effects, adverse effects

### INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) have proliferated as pharmacological interventions for numerous psychiatric disorders in both psychiatric and primary care settings. This level of unrivaled popularity is probably due to 1) the broad clinical efficacy of these drugs, which is ideal in clinical cases with psychiatric comorbidity; and 2) their relatively mild side effects (with the exception of sexual dysfunction). However, SSRIs may be associated with another unwelcome clinical side effect—behavioral and affective indifference. This clinical phenomenon has not undergone substantial research to date. However, we suspect that most practicing clinicians have, at some point in clinical practice, encountered a patient on SSRI therapy who reported the experience of apathy and/or emotional blunting. In this edition of *The Interface*, we discuss this unusual but not unheard of side effect of SSRIs.

## A SYNDROME OF INDIFFERENCE

In the published literature, SSRIs have been associated with a general syndrome of indifference. However, this meager literature appears to have separated into two general paths of description: indifference as a behavioral syndrome and indifference as an emotional syndrome.

**A behavioral perspective.** As a behavioral syndrome, the clinical feature of apathy or low motivation has been underscored in association with SSRI prescription. This potential side effect is apparently somewhat recognized. For example, on the internet's Wikipedia site,<sup>1</sup> apathy is openly noted as a potential side effect of SSRIs. In addition, behavioral apathy has been described in several case reports and in numerous patient internet blog sites.

What is apathy? According to Marin,<sup>2</sup> apathy is defined as the presence of diminished motivation in an individual—a development that is not attributable to a reduced level of consciousness, cognitive impairment (e.g., dementia), or emotional distress (i.e., depression). Reinblatt and Riddle<sup>3</sup> reinforce this definition of apathy by clarifying that the lack of motivation cannot be the result of sedation or depressive symptoms.

In highlighting this behavioral symptom, a number of authors have developed corresponding descriptive monikers for this syndrome, including “amotivational syndrome,” “apathy syndrome,” “SSRI-induced apathy syndrome,”<sup>4</sup> “SSRI-induced apathy,”<sup>3</sup> and “antidepressant apathy syndrome (AAS).”<sup>5</sup>

**An emotional perspective.** In contrast to authors who have emphasized the behavioral aspects of this syndrome, others have emphasized the emotional aspects of indifference. Within this emotional perspective, most authors clearly differentiate emotional indifference from depression.<sup>3</sup>

In defining the clinical features associated with emotional indifference, Opbroek et al<sup>6</sup> describe a diminution in emotional responsiveness.<sup>6</sup> Price and Goodwin<sup>7</sup> describe a reduction in emotional sensitivity as well as a sense of numbing or blunting of the emotions.<sup>7</sup> Price et al<sup>8</sup> note that affected patients oftentimes describe a restricted range of emotions, including those emotions that are a part of everyday life.<sup>8</sup> The preceding authors also describe a number of distinct emotional themes in affected patients, including a general reduction in the intensity or experience of all emotions, both positive and negative; a sense of emotional detachment; “just not caring;” and diminished emotionality in interpersonal relationships, both in personal and professional relationships. While some of these effects may be beneficial at times (e.g., the blunting of an anger response in a volatile patient), they may be detrimental at other times (e.g., emotional indifference at the funeral of a close family member).

**The unification of both features.** Note that both of these descriptive perspectives, behavioral apathy and emotional blunting, encompass the concept of indifference. So, perhaps a more inclusive clinical perspective is to conceptualize the SSRIs as capable of causing indifference, both on a behavioral level (i.e., decreased motivation) as well as on an emotional level (i.e., emotional blunting). In this broader vein, a more appropriate descriptive term for this syndrome might be *SSRI-induced indifference*.

## EPIDEMIOLOGY OF SSRI-INDUCED INDIFFERENCE

At the present time, there are no large-scale epidemiological studies of SSRI-induced indifference. Therefore, we have limited data on general

“I have experienced a side effect while taking the medication that has been surreal at times. I began to notice that I no longer cried when watching favorite movies that always had me grabbing for Kleenex by the handful. I no longer teared up when reading about or hearing of very sad events. At funerals, I literally felt my emotions being trapped inside of me. I would think, ‘I am so sad. I really need to cry to release all this emotion. The sadness physically hurts. Why can't I cry?’ So I guess the “miracle drug” does indeed have its drawbacks, but for me, the good outshines the bad.”

—Kathy C.

prevalence rates and no data on gender/age/racial distributions, differential rates (if any) among the various SSRIs, and/or adjunctive risk factors such as co-administered drugs, medical conditions, and/or psychiatric comorbidity.

As for prevalence rates, according to a study by Bolling and Kohlenberg,<sup>9</sup> approximately 20 percent of 161 patients who were prescribed an SSRI reported apathy and 16.1 percent described a loss of

**TABLE 1.** Clinical characteristics of SSRI-induced indifference

- Low insight in the afflicted, particularly in children and adolescents, with regard to behavioral symptoms (i.e., low motivation)
- Delayed or insidious onset
- Related to SSRI dosing, with higher doses being more likely to precipitate the syndrome
- Completely resolvable with a lowering and/or discontinuation of the SSRI

Note: SSRI=selective serotonin reuptake inhibitor

ambition.<sup>9</sup> In a study by Fava et al,<sup>10</sup> which consisted of participants in both the United States and Italy, nearly one-third on any antidepressant reported apathy, with 7.7 percent describing moderate-to-severe impairment, and nearly 40 percent acknowledged the loss of motivation, with 12.0 percent describing moderate-to-severe impairment.<sup>10</sup> In a third study, researchers examined 43 pediatric patients with anxiety disorders and noted that five percent of the study sample developed apathy while taking fluvoxamine.<sup>3</sup>

## ETIOLOGY OF SSRI-INDUCED INDIFFERENCE

The precise etiology of SSRI-induced indifference remains unknown. However, a number of investigators have proposed possible explanations. For example, Barnhart et al<sup>4</sup> suggest that this syndrome may be related to 1) serotonergic effects on the frontal lobes and/or 2) serotonergic modulation of mid-brain dopaminergic systems, which project to the prefrontal cortex. Likewise, Wongpakaran et al<sup>11</sup> suggest the possibility of frontal lobe dysfunction due to the alteration of serotonin levels.

## CLINICAL CHARACTERISTICS OF THE SYNDROME

To date, clinical experience suggests several characteristics of

this syndrome (Table 1). First, SSRI-induced indifference may be accompanied by the presence of low insight, particularly with the emergence of behavioral symptoms (i.e., low motivation) in children and adolescents.<sup>3,12</sup> Second, the onset of the syndrome may be insidious and delayed (i.e., there may not be the emergence of indifference at the onset of SSRI prescription).<sup>3,12</sup> Third, the syndrome appears to be related to SSRI dosing, with higher doses being more likely to precipitate a behavioral and/or emotional state of indifference.<sup>3,4</sup> Finally, the syndrome is completely resolvable by either lowering the dose and/or discontinuing of the offending agent.<sup>3,4</sup>

## EMPIRICAL STUDIES

As we noted previously, there are several case reports in the literature and three prevalence studies, but other types of empirical studies in this area are limited. Indeed, we could only locate three additional investigations. In a study of 15 patients who were being treated with SSRIs for major depression and drug-induced sexual dysfunction, 80 percent reported the blunting of emotions (Could sexual dysfunction be a potential marker of this syndrome?).<sup>6</sup> In a second study, which was undertaken to consolidate a clinical description of this syndrome and to develop a

symptom measure, Price et al<sup>8</sup> qualitatively examined emotional blunting and identified eight key themes.<sup>8</sup> Finally, Wongpakaran et al<sup>11</sup> examined two groups of elderly depressed patients on antidepressants, either SSRIs or nonSSRIs. Using apathy scales developed by one of the authors, findings indicated that those participants on SSRIs were more likely to report apathy than those on non-SSRIs.<sup>11</sup>

This handful of existing studies underscores the lack of large-scale clinical studies on the prevalence of SSRI-induced indifference, particularly with regard to emotional blunting (i.e., apathy has been more studied), in either psychiatric or primary care populations, despite the high prescription rates for these types of antidepressants.

## PSYCHOMETRIC ASSESSMENT OF SSRI-INDUCED INDIFFERENCE

There are no current clinically popular scales for the assessment of SSRI-induced indifference. The oldest available apathy scale is the Marin Apathy Evaluation Scale (1991).<sup>13</sup> This scale was developed to assess apathy in adults age 55 or older and is referenced in a number of studies on schizophrenia and neurological disorders, such as dementia. The scale is available in three versions: clinician, informant, and self-report. The clinician version is a semi-structured interview with both open- and closed-ended questions, takes about 15 minutes to complete, and requires training to administer. This measure has not been used in research with SSRI-induced indifference.

In their study, Opbroek et al<sup>6</sup> used the Laukes Emotional Intensity Scale, which is an 18-item, Likert-style, self-report measure that assesses current versus “usual” emotional status. This measure has

only been used in one published study.

As a scale under development, the Oxford Questionnaire of Emotional Side Effects of Antidepressants (OQESA) is a 26-item, Likert-style, self-report scale that explores respondents' emotional experience over the past week.<sup>7</sup> This measure explores a general reduction in emotions, a reduction in positive emotions, emotional detachment from others, and feelings of not caring. Respondents are also asked to what extent they believe their antidepressant is responsible for these emotional symptoms.

### CLINICAL MANAGEMENT

Because this syndrome is commonly under-recognized by both patients and clinicians, we recommend advising patients who are about to embark on a course of SSRI treatment about the possibility of SSRI-induced indifference. Following the education of patients as well as their families, we suggest routine monitoring by the clinician during medication follow-up appointments.

If the syndrome emerges during treatment, according to Barnhart et al,<sup>4</sup> there are three general clinical strategies to consider. The first strategy to consider is a dosage reduction of the SSRI, if clinically feasible (i.e., if the reduction does not precipitate an exacerbation of the previous psychiatric symptoms). As a second strategy, the clinician may want to consider the addition of a second drug. While this suggestion has little substantiation, there is one case report in which the addition of bupropion reduced this unwanted side effect.<sup>12</sup> Finally, the clinician may want to consider a switch to an antidepressant in another drug class, such as an serotonin–norepinephrine reuptake inhibitor (SNRI).

### CONCLUSIONS

SSRIs have been associated with indifference, both in behavioral terms as well as emotional terms. While the literature has separated out these two symptom clusters, from a clinician perspective, it seems feasible to reunite them and describe them as SSRI-induced indifference. The epidemiology and etiology of this syndrome is largely unknown. Few empirical studies are available, but SSRI-induced indifference is likely to be under-recognized (e.g., it is characterized by low insight in those afflicted, particularly children and adolescents), have an insidious and delayed onset, be related to dosing, and completely resolve with a dose reduction or discontinuation of the SSRI. As for treatment strategies, possibilities include a dose reduction in the SSRI, augmentation with another medication, or switching from an SSRI to a non-SSRI. Clearly, given the prevalence of SSRI prescription, this is a topic of relevance for both mental health and primary care clinicians.

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“I have noticed that I am devoid of emotions most of the time. One of my dearest friends is dying from metastatic breast cancer, and I am finding that I am not able to cry or experience any emotions about it. I know that I want to cry, but I can't. I want to be able to express my anger at the unfairness of what is happening to her, but all I feel is numbness. I would describe myself as a robot who is going through the motions, but I have no feelings. I believe that I am having these feelings of apathy and numbness because...these are some potential side effects of this medication. I am thankful that there are medications available for people with depression because it isn't something that a person can just “get over,” but it is very frustrating to be aware of the fact that my friend is dying from cancer and the medication won't allow me to grieve for her.”  
—Cheri H.

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