tom 15, nr 1, 57–61

ISSN 1732–9841

Sławomir Murawiec
Centrum Terapii Dialog, Warsaw, Poland

Case study in *Stahl's Essential Psychopharmacology* — proposition to look at the same problems from a different angle

Introduction

Stephen M. Stahl is one of the most widely internationally respected pharmacologists whose excellent books and articles are known around the world. Schemes, diagrams, and above all graphic illustrations of receptor binding profiles of psychotropic agents provide invaluable help in understanding psychopharmacology. Following this respect for Stephen Stahl's works, at one of the scientific conferences I have bought his book with case studies ("Case studies: Stahl's essential psychopharmacology"), getting with great pride Author's autograph. After some time I started reading this book and going through the first chapter I experienced growing curiosity. When reading the case of the first patient, I thought how precise and complete description it contains. The patient described there is close to what I know from my own everyday practice. So I reflected: „I have many patients like the person described here". However, in the course of further reading, I noticed we are looking at the same problems from a different angle. Based on the same case description, the different associations appeared in my mind, than those proposed in the book. That does not mean that my conclusions challenged what Author wrote, however were moving in a different direction. I would think of
events during the treatment of this patient in another context. It needs to be stressed that such comparative thinking is possible thanks to a full description of the case provided by the Author. But I propose that the same clinical data could be viewed from another perspective.

Address for correspondence:
Sławomir Murawiec
ul. Słomińskiego 19/523, 00–195 Warszawa, Poland
tel.: +48 606 288 260
e-mail: smurawiec@gmail.com

A case description

The commented here chapter is entitled „The man whose antidepressants stopped working" [1]. According to the author, it raises a clinically important question as to whether depressive episodes become more difficult to treat and are more likely to occur with time, and its essential content circles around the dilemma when to stop giving antidepressants and what to do if drugs that have been effective in the past, currently do not work.
The case concerns a man aged 63 in his most severe so far episode of depression and anxiety.
Previous episodes in the patient:

1) At age 42 — alprazolam, clonazepam and finally sertraline 100 mg/day were given with significant improvement after 2–3 months. The drug was discontinued after 6 months.
2) The second episode when he was 52 years old. Treated with paroxetine without any improvement in mental state, then sertraline 150 mg and clonazepam. Symptoms subsided after 2–3 months, he stopped taking sertraline after a year. There was a sexual dysfunction while taking sertraline.
3) The third episode at the age 58. Treated with bupropion without improvement in mood, then sertraline was re-activated and improvement after 8 weeks of treatment occurred. After one year he stopped treatment.
4) The fourth episode at the age of 61. Venlafaxine was given for quick relief of symptoms. Treatment continued for a year.

5) Fifth episode treated with venlafaxine 75–150 mg, without improvement after 8 weeks, followed by 375 mg also without a positive result. Then after 4 months the treatment was supplemented by dextroamphetamine 20 mg daily, buspiron 30 mg daily, clonzapam 4 mg daily and lorazepam 4 mg daily. Only a partial improvement in mental status was achieved. Treatment had been changed into sertraline 200 mg per day but no improvement was observed between 12th and 15th month of treatment. No improvement after 15 months of treatment as well. Then mirtazapine 15 mg was added daily, lorazepam was withdrawn, clonazepam dose increased, dextroamphetamine dose reduced. Sertraline was administered at a dose of 200 mg. Some improvement occurred in 18th month of treatment, increased dose of mirtazapine to 30 mg, quetiapine 300 mg added daily. Unfortunately, there was no improvement in the patient's condition. Part of the drugs (sertraline, mirtazapine, dextroamphetamine) were discarded and seven days after transcutaneous selegiline was recommended. After 4–5 weeks the patient began to feel better, he could even make the impression of being hypomanic, but his condition was assessed to be expression of joy that he felt better after 2 years of the episode.

As indicated by the author, the remission periods were gradually shortened and lasted respectively 9.5 years, 5 years. 2 years. 1 year. The first four episodes were relatively easy to treat and the patient underwent complete symptomatic remission. Supportive treatment lasted from several months to a year. In contrast, in the course of the fifth episode, resistance to pharmacological treatment appeared and lasted for 2 years. Responding to treatment with SSRIs in the first 3 episodes and the SNRI group drug in the fourth episode brought rapid and effective help to the patient. On the other hand, the fifth episode was no longer so prone to treatment and only after two years of pharmacotherapy the patient responded to the treatment with selegiline.

The same story outlined above, however, is also depicted by the author in parallel, in the additional context. We learn that at age of 42 years the patient began to manifest depressive and anxiety symptoms after the first episode of atrial fibrillation. He was afraid that something bad might have happen to him and he was afraid of death. After hospitalization for atrial fibrillation, treated pharmacologically, he felt depressed, anxious, feeling „butterflies in his stomach, "and reported the impression" as if the whole body was plugged into the electrical circuit." He also revealed during this and subsequent episodes suicidal thoughts, but what is worth noting is the contradiction with the above-mentioned fear of one's own life. Significant episode of atrial fibrillation coincided with the death of the patient's mother. Life events preceding subsequent depressive episodes are reported in Table 1.

The author also highlights the biological aspects of returning depressive episodes and indicates that there is a likelihood of a change in the brain, with the loss of volume of the hippocampus and/or prefrontal cortex due to the previous 4 and the current episode of depression and anxiety. He also points out that precisely for this reason the fifth episode may be resistant for pharmacotherapy which has been effective so far. In the table summarizing the entire chapter Stahl draws attention again to biological factors such as cortico limbic connections disturbances and loss of hippocampal volume in depression as well as the beneficial effects of pharmacotherapy in this regard. Medications can, by influencing the neuroplasticity and secretion of trophic factors in the brain, normalize the brain activity and reverse the abovementioned adverse changes.

In conclusion, Stahl writes that there is no doubt that patient should be treated with antidepressant support after a third episode of depression, which would probably prevent the 4th and 5th episodes, and the development of drug resistance. This is the main conclusion of this case study. However, he also indicates that the patient is a very

Table 1. Life events preceding subsequent depressive episodes in the described patient

First episode	First episode of atrial fibrillation and death of mother
Second episode	Partial early retirement, he again felt that something bad might have happen to him and was afraid of what it meant for him that his life was over
Third episode	No data
Fourth episode	Once again retirement, the patient returned to work, succeeded and retired. Again there were concerns about mortality.
Fifth episode	Problems in marriage

religious person and does not believe in psychotherapy. The author notes that perhaps more effort should be put in encouraging him to undergo psychotherapy in order to cope with issues related to his mortality and reactions to psychosocial stressors.

What I paid attention to

Based on the same information outlined above, while consulting this patient I would point out some of the elements of the first episode of depressive mood. In the period immediately preceding the deterioration of his well-being the patient's mother died, and he himself had the first episode of atrial fibrillation. After these events, he felt that something bad might have happen to him and he was afraid of death („felt vulnerable and afraid of death"). So if looking at the symptoms of the patient in this context, it can be seen that there are some elements which in the International Classification of Diseases ICD-10 would be included in the category of hypochondria disorders and in the DSM-5 illness anxiety disorder (DSM-5 300.7). Probably, after the death of the mother and his own cardiac episode, the following thought occurred to the patient: "Me too, can die, and I am mortal. I can die at any moment on a heart failure". This thought could be accompanied by the anxiety described in the chapter, and this anxiety found its expression in the "butterflies in the stomach". It has probably been with the patient all the time in the later stages of his life. Concerns about the disturbance of heart work in the context of own mortality were reflected in the idea of connection to the electrical circuit. This may reflect the fear of disconnecting or turning off this "circuit", which would inevitably lead to death.

With respect to the first episode, the mother's death might also have been relevant, which raises the question of mourning. Thus, to conclude, the specific events mentioned in the case report indicate in my view that the patient had persistent fear of death (for cardiac reasons), which justifies the diagnosis of illness anxiety disorder (DSM-5). This aspect is clearly reflected in the description of the case, but is omitted in the concluding part. On the other hand, he is constantly present in reference to the second and fourth episodes. When describing the second episode, we find out that retirement meant for the patient that "his life is over", and in the fourth episode we find the phrase "brought up worries about his mortality again". As can be presumed, after the episode of atrial fibrillation, the patient was afraid of dying throughout the years, and these fears were updated and activated by various life events. These events related to professional work were so important to the patient that they triggered depressive-anxiety symptoms.

Taking into account this point of view, the fifth episode of depression differs from previous ones. It was provoked this time not by the fear about the patient's own life but by the problems of the patient's marriage. So it may have had quite different character. Obviously, there must be a reservation that this is only a presumption, still it seems to be justified in clinical and scientific data [2]. If so, the chronic problems in a matrimonial relationship at the age of 63 can vary considerably from the past experiences of fears about health and life as well as problems related to retirement. Especially if they are chronic. In this context, we can take another way of counting depressive episodes in the patient's life — the first four episodes belonged to one group, linked to mortality and death. The fifth, the heaviest and longest episode, was triggered entirely by other issues, namely marriage problems. It could have been so completely different from the previous ones — there could be more elements in the course of events supporting low mood and other symptoms of depression, and therefore it could be more prolonged and not prone for treatment that was previously effective. From this point of view we can also look at differences in the efficacy of the drugs used. If we take into account the continuity between episodes 1–5, the patient in the fifth episode has unexpectedly failed to respond to the clinical improvement of the drugs administered so far. But if we consider the fifth episode to be completely different and de facto the first episode of the new process, it puts drug resistance in a completely different light. Drugs that have been effective so far this time do not work out because the current state of the patient's psychiatric condition is, despite similarities, different from the previous ones. In the description of the fifth episode, we learn that "some of the symptoms were as before", which may also mean that some of them were different from the previous ones. And above all, the author points out that the response to the treatment was unusual, that is, it did not occur in the situation of the use of drugs, the application of which had previously brought rapid improvement. Pharmacological treatment can also be seen in this case in two contexts. Namely, not only from the formal point of view of indications for drug use in depression, but also from the point of view of the effects of emotional responses, which has been repeatedly raised in the scientific literature [3–5]. SSRI drugs lead to a certain state of subjective perception and reported by the treated persons state of indifference. In addition, sertraline, by acting on sigma receptors, exhibits anxiolytic effect [6]. Analogical thinking can be applied in case of venlafaxine used in some episodes of the patient described here. This state of emotional distance, indifference, could prove to be extremely clinically useful in the context of the above-

-described patient's anxiety. The patient could, from the perspective of subjective experience, stop worrying about these issues and be afraid of them.

Here I would like to add that I have no experience with the use of selegiline in depressive disorders, so I have no way of formulating a comment on this type of treatment in the above-mentioned subjective dimensions.

Bupropion was used in the third depressive episode of the patient described here, but its administration did not bring clinical improvement. The choice of this drug was dictated by the fact that the patient reported sexual dysfunction during sertraline treatment. In this context, we can make comments about ways of thinking of the treatment of depression. If in the treatment of depression we can use any drug out of the pool of available antidepressants, the choice of bupropion is justified in such a way of thinking — as an antidepressant that does not cause sexual dysfunction [7]. However, if we take into account the needs of the patient, the profile of his symptoms and expectations from therapy, then the activating effect, the absence of anxiolytic activity and, above all, the lack of action giving emotional distance to the stressors (sometimes perceived as indifference) allows to expect that in such as the described case bupropion will not prove effective, what is confirmed in the available description. It can briefly be pointed out that, in such case as described by Stephen Stahl, different profile of the antidepressant effect will be more tailored to the needs of the patient.

Stephan Stahl writes in his summary that the patient should receive continuous antidepressant treatment indefinitely. It is not the purpose of this work to make a polemic with this recommendation. Perhaps the chronic administration of SSRIs, by their effect on emotional reactivity, would allow the patient to change the way of functioning in the marriage, which would not lead to difficulties in the relationship preceding the fifth episode.

The important issues raised in this chapter concern the impact of depressive episodes on brain biology. There is no way to disagree. On the other hand, a closer look would require the suicidal ideations in the patient. From the description we found out that the patient is a religious person, which may be a protective factor from committing suicide [8], but we also learn that in many situations he expressed his fear of death. Perhaps the suicidal thoughts of the patient were secondary to fear of death, as in those patients with a health and life-anxiety who reveal the following way of thinking: "let it be over now, if I'm going to die, let me die now so as not to".

Conclusions

In conclusion, I would like to point to two perspectives in which pharmacological treatment of psychiatric disorders and psychotropic drugs may be seen. They could be defined as the following perspectives:

1) internal and external way of looking at the symptoms reported by the patient;
2) focused on diagnosis and focused on "psychopharmacology of a specific drug", which is raised by Yeomans *et al.* [9]

With regard to the first of these points, an "external" approach is based on the diagnosis, for example the diagnosis of depressive and anxiety disorders, and the use of any drug from a pool of substances that have formal indications for the diagnosis in question. In the "internal" approach, the diagnosis takes into account also the content and individual context of the patient's complaints and the need for drug selection that may arise from the consideration of these aspects.

With respect to psychotropic drugs, Yeomans *et al.* [9] postulate alternation of thinking about drug action, from taking them as specific to a given disorder (ascribed to a specific diagnosis) to an approach based on "psychopharmacology of a specific drug". In the approach proposed by these authors, in the center there should be the drug, more specifically its effect on mental processes (or wider psychophysiological processes). In this context, we can think of the effect of the drug like this: how this way of action can be used to carry on an effective psychopharmacology of people experiencing disruptions of those processes into which the effect of the drug is directed. According to these authors, the "drug specificity" approach is based on assessing whether the drug's effects on mental activity and behavior can be useful to the patient (taking into account the patient's specific life situation). An example of the application of this way of thinking are the comments made above about the action of sertraline in the case described. This drug, perhaps through its action causing emotional distance and evoking anxiolytic effect, has proved to be effective in treating the first four episodes of a patient's depression.

References:

1. Stahl SM. Chapter one: The man whose antidepressants stopped working. In: Stahl SM. ed. Case studies: Stahl's essential psychopharmacology. Cambridge University Press, New York 2011: 1–13.
2. Rantala MJ, Luoto S, Krams I, et al. Depression subtyping based on evolutionary psychiatry: Proximate mechanisms and ultimate functions. Brain Behav Immun. 2017 [Epub ahead of print], doi: 10.1016/j.bbi.2017.10.012, indexed in Pubmed: 29051086.
3. Price J, Goodwin GM. Emotional blunting or reduced reactivity following remission of major depression. Medicographia. 2009; 31: 152–156.
4. Opbroek A, Delgado PL, Laukes C, et al. Emotional blunting associated with SSRI-induced sexual dysfunction. Do SSRIs inhibit emotional responses? Int J Neuropsychopharmacol. 2002; 5(2): 147–151, doi: doi:10.1017/S1461145702002870, indexed in Pubmed: 12135539.
5. Goodwin GM, Price J, De Bodinat C, et al. Emotional blunting with antidepressant treatments: A survey among depressed patients. J Affect Disord. 2017; 221: 31–35, doi: 10.1016/j.jad.2017.05.048, indexed in Pubmed: 28628765.
6. Stahl SM, Lee-Zimmerman C, Cartwright S, et al. Serotonergic drugs for depression and beyond. Curr Drug Targets. 2013; 14(5): 578–585, indexed in Pubmed: 23531115.
7. Murawiec S, Jakima S. Bupropion — skuteczny lek przeciwdepresyjny o korzystnym profilu działania w sferze seksualnej. Seksuologia Polska. 2007; 5: 83–88.
8. Stack S. Religion and suicide acceptability: A review and extension. Suicidologia. 2015; 18(1), doi: 10.5617/suicidologi.2181.
9. Yeomans D, Moncrieff J, Huws R. Drug-centred psychopharmacology: a non-diagnostic framework for drug treatment†. BJPsych Advances. 2018; 21(04): 229–236, doi: 10.1192/apt.bp.114.013094.