Case Report

Psychotropic Drugs Discontinuation Syndromes in Clinical Practice

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Abstract. We focused our analysis on discontinuation syndrome, a frequent but unrecognised entity in psychiatric practice, which could be responsible for a great deal of misdiagnosis and treatment errors. If benzodiazepines and anticholinergics are well known for their potential of inducing discontinuation syndromes, there was less research regarding antidepressants and antipsychotics from this point of view. Theoretical data as well as clinical vignettes are presented here in an attempt to underline the necessity for inclusion of this syndrome in differential diagnosis and to show several ways to deal with it.

Keywords: discontinuation syndrome, antidepressants, antipsychotics, benzodiazepines, anticholinergics

Since the discovery of the first antidepressant, imipramine, a variety of discontinuation syndromes were related to psychotropic drugs, including substances like benzodiazepines, tricyclic antidepressants, monoamine oxidase inhibitors (MAOI), selective serotonin reuptake inhibitors (SSRI), serotonin and noradrenaline reuptake inhibitors (SNRI), anticholinergics, typical and atypical antipsychotics. Also there are many terms describing this kind of pathology, resulting in a terminological confusion, according to D.A. Ciraulo and O. Sarid - Segal “some authorities reserve the term discontinuance syndrome for withdrawal syndromes that develop with therapeutic agents to distinguish physiological dependence that develops throughout the course of treatment from dependence that develops from misuse of the drug” [1]. While the term “withdrawal” is associated with addiction patterns of use both in most of the psychiatric literature (see DSM IV TR or ICD 10 criteria) as well as in the lay people’s perception, “discontinuation” syndrome seems less pejorative and more accurate, since antidepressants and neuroleptics are not drugs of abuse.

The most used antidepressant drugs involved in the discontinuation syndromes category are the SSRI class. These drugs (sertraline, paroxetine, citalopram, escitalopram, fluoxetine and fluvoxamine) produce a syndrome characterized by dizziness, nausea, diarrhea, irritability, anxiety, insomnia, tremor, sweating, vertigo, ataxia, paraesthesia in case of abrupt interruption. 35% to 78% of individuals who received an SSRI for several months experience such a discontinuation syndrome [2]. The same authors mentioned that symptoms are usually mild and short-term, but occasionally can be severe and long lasting. J. Zajecka et al. showed that discontinuation of selective serotonin-reuptake inhibitor therapy may last up to three weeks after interruption of treatment, and may be relieved by restarting antidepressant therapy [3].

The physiological mechanisms are sustained by double blind studies in which SSRIs are substituted with placebo for a short period of time [4]. Paroxetine is associated with a high degree of discontinuation symptoms while fluoxetine has the lowest rate of incidence [5]. Pharmacokinetic profiles of the SSRIs were supposed to correlate with the appearance of the discontinuation syndromes, meaning that the lowest incidence in fluoxetine treated patients is an artifact due to the late onset syndrome of discontinuation. Fluoxetine has a half-life in chronic administration of 4-6 days and its active metabolite, norfluoxetine, of 4-16 days while paroxetine reach a 21 hours half-life. Still, in a study designed by Zajecka et al. [3], there was no evidence of a clinically important discontinuation syndrome in the first 6 weeks after fluoxetine interruption.

Case presentation 1

A 32 year-old woman with previous record of unipolar depression, who received clomipramine 250 mg daily for about 4 months, was switched on paroxetine 40 mg daily because of a decreasing therapeutic response. After a 6 months period with significant improvement in depressive symptomatology, paroxetine was discontinued in a week, with 10 mg decrease at every 2 days. This patient was admitted to our clinic second day after complete removal of paroxetine from the treatment. At the admission, patient presented with lethargy, paraesthesia, tremor, sweating, nausea, anxiety, depression and insomnia. Differential diagnosis included recurrence of the depressive episode but it was invalidated due to the immediate onset of symptoms after the drug cessation and the cluster of characteristic features of discontinuation syndrome. We chose to reintiate paroxetine in 20 mg daily with a slower decrease, meaning 5 mg each week. There was no necessity to initiate another drug during the gradual paroxetine discontinuation or after the complete elimination of the antidepressant. Patient’s evolution was satisfactory and symptomatology that provoked the admission remitted after reintiating the drug. Patient was discharged from our clinic after a week and continued to decrease the paroxetine according to the plan.

Tricyclics discontinuation syndrome is different from the SSRI because of the lack of sensory abnormalities (mainly
Case presentation 2

A 45-year-old woman with a history of variety of tricycles drug treatments for a recurrent major depressive disorder (amitriptyline, doxepin, imipramine) was switched to fluoxetine because of a concomitant cardiac pathology. This change in treatment was realized while patient was hospitalized in a cardiology clinic and required an immediate discontinuation in imipramine administration due to a lateral myocardial infarction. After two days of switched treatment, anxiety increased, depressed mood became evident, fatigability, insomnia, and gastrointestinal symptoms like nausea and flatulence and lack of appetite appeared suddenly. We concluded there was a discontinuation syndrome due to the switch in drugs with different pharmacokinetic properties and no additional treatment was added. Also, adverse events of fluoxetine administration overlapped in this context. Symptoms vanished gradually over the next three days and the general status improved.

MAO1 discontinuation syndrome is not a rare clinical entity and has as a confusional acute state and possibly paranoid delusions and auditory or visual hallucinations [6]. Also, a worsening in depressive phenomenology, anxiety increasing up to panic attacks or depersonalisation and derealisation could occur. Generalized seizures following tranylcypromine discontinuation are reported by Vartzopoulos and Krull [7].

Venlafaxine and mirtazapine are related to rare discontinuation syndromes which include manic or hypomanic symptoms in patients with bipolar or unipolar depression [8,9]. Discontinuation syndromes with hypomania tend to resolve itself without treatment or after restarting the initial antidepressant. Akathisia is observed rarely after venlafaxine discontinuation [10] and disappear quickly after reintiating the treatment. Irregularities in blood pressure, visual and auditory hallucinations are reported after venlafaxine discontinuation.

Case presentation 3

Twenty-two years-old man, diagnosed with major depressive disorder was treated with venlafaxine 225 mg daily for about 12 months, with favourable outcome. After that period, patient stopped his treatment abruptly without consulting to a specialist. A discontinuation syndrome was diagnosed based on the following symptomatology: marked irritability, restlessness, auditory hyperesthesia, anxiety, insomnia and fatigability. We observed variations during the daily monitoring of blood pressure, which stopped after the reintialisation of venlafaxine in 150 mg per day. Patient presented to our clinic two days after discontinuation and symptomatology remitted after three days of treatment. We used a tapering of treatment with 37.5 mg venlafaxine per week. No symptoms were observed neither during the 7 day of hospitalization nor during the 4 week of outpatient monitoring.

Regarding the pharmacological basis of antidepressant discontinuation syndrome, there are various hypothesis related to pharmacokinetics (rate of metabolisation and elimination of drug) and pharmacodinamics (both therapeutical and side effects). If we consider the first aspect of the problem, genetic background and comorbid disorders are of great importance. The synaptic neurotransmitter release and receptoral adaptation represents main components of the pharmacodinamic mechanisms. All these features have individual variability and could explain why duration, severity and symptomatology are so different. SSRI discontinuation syndrome may be the result of serotonin deficiency and we know the importance of this neurotransmitter in the appearance of mood disorders (5HT1A), motor activity disturbances (5HT1B), gastrointestinal symptoms (5HT2B, 5HT3), cognitive (5HT3, 5HT4) and circadian rhythms (5HT7) problems. Differences in the half-life and active metabolites are responsible for variations in the discontinuation syndrome incidence (fluoxetine vs. paroxetine, for example). Regarding the tricycles, discontinuation syndrome manifestations are, at least partly, due to the cholinergic rebound: abdominal pains, nausea and intestinal transit disorders. However, the MAOI discontinuation mania or hypomania syndromes are involved with hyperdromingeric mechanisms [11].

We consider that there are several factors to be considered in general treatment of a discontinuation syndrome: the severity of symptomatology, the recommendation for further antidepressant treatment, the patient’s perspective over the manifestations (how does he or she deal with this) and the clinician’s understanding of the pathology (how does he consider this fact will interfere with patient’s well being or with the therapeutical alliance). We consider either reintroducing the antidepressant previously used and taper it off slowly or, if the symptoms are mild and patient accept them as transitory, not to intervene pharmacologically and to reassure the patient about the nature and duration of this syndrome. Manic symptoms following discontinuation of antidepressants are treated with antipsychotics in moderate dosages while hypomania resolved usually after reintitiation of the drug used [12,13]. In MAOI discontinuation syndrome with psychotic or confusional states, antipsychotics could be used with or without the initial drug.

Prevention of this syndrome includes gradual discontinuation of antidepressants at the end of the treatment schedule, especially where drugs like SSRIs (less in the fluoxetine administration), tricycles, MAOI or venlafaxine are used. Attention to other factors like side effects of a new antidepressant in a switch strategy, non-compliance to treatment, recurrence of depression and adverse events from other simultaneous administered drugs etc. which interfere with a correct diagnosis should be considered.

Benzodiazepines discontinuation syndromes include three types of syndromes: relapse, rebound and withdrawal [1]. Relapse is defined as the return of symptomatology after treatment was stopped. This is the case in many anxiety disorders, which tend to reappear if benzodiazepines are discontinued. This is the reason for the actual trend in treating anxiety disorders using less benzodiazepines but antidepressants from the new generations.

Rebound is an intensification of the original symptoms at the end of treatment. Within several weeks of drug discontinuation, a worsening in symptomatology is observed for a variable period (days to weeks). After this interval the
general status returns to baseline. If we use benzodiazepine with short half-lives like alprazolam, we may observe a daily aggravation of symptoms between dosages. This is why patients with such treatment need to take this kind of medication more frequent (in 3 to 4 daily administrations) without being suspects for misuse.

Withdrawal syndromes include new symptoms and appear within hours to days of discontinuation if short half-life benzodiazepine is used and to weeks if a longer half-life drug is used. Duration for such syndromes varies also with the half-lives. Tapering off the drug in a slowly and controlled manner reduces the risk for withdrawal. This phenomenon is a natural consequence of receptoral adaptation to chronic drug use. When benzodiazepines are administered daily, benzodiazepine receptors downregulate. The excitability of neurons is increased, resulting in tremor, myoclonus, and seizures. Slower benzodiazepine withdrawals permit an upregulation of the benzodiazepine receptors and avoid clinical hyperexcitability symptoms. This syndrome is treated with reinitiation of benzodiazepine used in the same dose and tapering off more slowly. An alternative is introducing a longer half-life benzodiazepine instead and gradually withdrawing this second drug. When doses of alprazolam previously administered for a long period is tapered off less than 1 mg threshold, benzodiazepine receptor has a paradoxical downregulation involved in rebound or withdrawal syndromes. Substitution with clonazepam facilitates withdrawal of the dosages under 1 mg daily but some clinicians sustain that clonazepam does not control alprazolam withdrawal better [14].

Case presentation 4

A 27 year-old man received from his GP treatment with alprazolam for a panic disorder. Patient was switched on paroxetine with abrupt discontinuation of previous treatment. Immediately after this change of drugs, patient presented tremor, sweating, nausea, anxiety, and thoracic pains and was admitted to a general hospital with a suspicion of myocardial infarction. All the laboratory analysis and para-clinical explorations were normal and a psychiatric exam was recommended. It was decided to reinitiate alprazolam in parallel to paroxetine with slower decrease in benzodiazepine dose. Because the last dose of alprazolam received by the patient was 1 mg daily, a rate of 0.25 mg per week was considered satisfactory. During the next 6 months, patient received paroxetine in 30 mg daily dose and presented no aggravation of anxiety disorder when alprazolam was completely removed from his treatment.

Anticholinergic discontinuation syndrome is due to muscarinic antagonism in the periphery-cardiovascular, gastrointestinal, autonomic and urogenital systems effects of this class of drugs. Patients tend to abuse these substances because of drug-induced euphoria, most commonly trihexyphenidyl that is the most stimulating in this class.

There is a cluster of symptoms, which are most common in the anticholinergic discontinuation syndrome. If trihexyphenidyl is abruptly discontinued; anxiety, difficulty in speaking or swallowing, restlessness or akathisia, dizziness or lightheadedness when getting up from a lying or sitting position, rigidity of arms or legs, loss of balance control, muscle spasms, especially of face, neck, back, trembling of hands, sleep problems, twisting movements of body could appear. If benztropine is discontinued, same cluster of symptoms could be diagnosed as a discontinuation syndrome.

Most of the conventional antipsychotics are involved in discontinuation syndromes [11,15]. An important issue is the differential diagnosis between symptoms of psychotic relapse and symptoms of discontinuation syndrome. A metanalysis realised by Dilsaver and Alessi [16] performed in selected patients within the first seven days of discontinuation from typical neuroleptics in order to differentiate the two kinds of pathology. The most common symptoms were nausea, vomiting and anorexia. Also, diaphoresis, headache, insomnia, restlessness, anxiety were symptoms of discontinuation. These symptoms appeared within the first four days without treatment and vanished gradually in one to two weeks. In a study realized by R. Battegay [17], a group of 88 patients that discontinued treatment in a double-blind, placebo-controlled manner. As a result, 68% developed withdrawal symptoms, especially dyskinesias, dystonic syndromes, sweating, vertigo, tachycardia, headaches, nausea, vomiting and insomnia. Recorded symptoms were so severe in 52 % of the patients that treatment had to be restarted in a week.

Clozapine is an atypical antipsychotic agent that provokes a discontinuation syndrome starting within two or three days, usually in the first two weeks from treatment cessation. The symptoms included in this syndrome are anxiety, insomnia, motor restlessness or mute withdrawal, confusion, diaphoresis and nausea [18]. Also, it can induce movement disorders, tics and Tourettes’ like syndromes. Alleged mechanisms for discontinuation syndromes of clozapine are the effects of drug on receptors (dopaminergic, serotoninergic, histaminergic, alpha-adrenergic and muscarinic) and up-regulation of these receptors during chronic administration. Clozapine has a strong anticholinergic activity and, when its administration is stopped, determines nausea, abdominal cramps, insomnia, anxiety, reflecting a cholinergic rebound [19]. Clozapine’s effects on D2 receptors and supersensitivity of GABA receptors are involved in causing motor symptoms when clozapine is discontinued [20].

Clozapine discontinuation could lead to rebound psychosis but it is unclear to what extend these symptoms are part of the cholinergic rebound, represents a reemergence of psychosis after drug cessation or it is a phenomenon characteristic to clozapine’s discontinuation. Some authors [21] argued that displacement of clozapine from D2 receptors by endogenous dopamine caused a rapid relapse of psychosis. The swift dissociation time of clozapine at D2 receptors may disguise a higher D2 occupancy than that estimated with receptor imaging studies and this may predispose to rapid psychotic relapse after withdrawal. Meltzer [22] suggested that rebound psychosis might reflect serotoninergic receptor alterations that occur while clozapine is administered, with a hyperserotoninergic state occurring after clozapine discontinuation.

In differential diagnosis, the time elapsed until symptom onset, previous evolution of patient under treatment and
presence of physical symptoms are of great importance. Antipsychotic discontinuation syndrome occurs in the first two weeks of treatment cessation but a recurrence is rare in this interval. If a patient under treatment is recently withdrawn from antipsychotics, they probably suffer a discontinuation syndrome. Nausea, headaches, abdominal cramps influence the diagnosis toward a discontinuation syndrome as physical symptoms does not occur frequently in a rebound psychosis.

Patients included in a switch procedure should be warned about the risk for discontinuation syndrome. Many of these syndromes are mild and short-lived and rarely necessitate treatment. Symptomatic treatment, like anticholinergics for cholinerigic rebound, could be recommended. If the symptoms are severe and or persistent, restarting the antipsychotic may be necessary.

Case presentation 5

A 40 year-old man with many previous admissions for chronic schizophrenia, paranoid type was referred for a psychiatric exam with symptoms of nausea, headaches, diaphoresis, anxiety, insomnia, restlessness, auditory hallucinations and persecutory type ideas of reference. This patient had stopped his treatment (clozapine 300 mg daily) abruptly without consulting to a specialist and developed these symptoms gradually. Presence of physical symptoms and the short interval from clozapine discontinuation indicated a high probability for a discontinuation syndrome. Patient was admitted to our clinic and clozapine treatment reinstated. We monitored this patient’s evolution for two weeks and physical symptoms vanished while his psychological status was improving.

Conclusion

In conclusion, the discontinuation syndrome is an important clinical entity, which should be considered in the differential diagnosis whenever an antidepressant, antipsychotic, benzodiazepine or anticholinergic drug is withdrawn from treatment. However the pharmacological mechanisms of this syndrome are not completely known, many factors are involved: genetic determinism for metabolism enzymes, receptor processes (up or down regulation), co morbid disorders, individual sensitivity to a particular drug etc. It is important to eliminate factors like noncompliance to treatment, effects due to other simultaneously administered drugs and recurrence of certain pathology. This syndrome could be mild and transient, necessitating only a symptomatic treatment or no medication, but it could also be intense and it might be necessary to reintitate the previously administered drug for the clinical improvement.

References