Motor Symptoms While Switching Antipsychotics: Should We Taper or Increase The Dose?

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Dear Editor,

Rebound syndromes are well described among several drugs, not only psychotropics. A key element to suspect them is that full manifestations of this phenomenon occur after a given period that depends on the drug’s half-life (1). Strictly within antipsychotics and their M1 cholinergic receptor blockade, switching from a high- to a low-affinity drug can induce cholinergic rebound, with symptoms like malaise, nausea, vomiting, diarrhea, sialorrhea, extrapyramidal symptoms and akathisia (2). We know, for example, that abrupt clozapine withdrawal has been associated with cholinergic rebound (3) as well as with serotonin syndrome (4). PubMed database (last search on 02/15/2016, search terms “cholinergic rebound AND antipsychotics”, with no time limit) shows 27 results for this topic: 04 case reports, 09 review articles, and 02 randomized controlled trials (only one specifically for cholinergic rebound). In the current case, cholinergic symptoms were observed while switching between typical antipsychotics.

The present case is about a 28-years-old male, who started to use drugs when he was 15, mostly marijuana (creepy or high red, for a daily consumption of 3-4 cigarettes). He also used cocaine (about 1g/week) from 20 to 27 years old. For the moment of these symptoms (that is, for the current admission), he had more than six months without consuming any drug, confirmed by doping. No comorbidity with other medical/psychiatric conditions is reported. He has three prior admissions to the psychiatric hospital, all of them because of psychotic symptoms. One of those was a manic episode with psychotic symptoms (like singing for hours in his room, saying that there was a live worldwide broadcast of this; hostile attitude toward his brother, whom he considered was planning to take some biological samples from him to make experiments; walking miles from home, trying to escape, etc). Since doping showed THC, and those psychotic symptoms rapidly improved with haloperidol, all of them were attributed to drug abuse. When psychotic and mood symptomatology are improved, a prominent narcissistic personality emerged. No other neuroleptic but haloperidol was used. In the particular admission of the manic episode, diagnosis workup could not be finished because his family signed to take him out from the hospital, despite medical recommendations. Now admitted because of a new manic episode with psychosis, initially treated with valproic acid (500mg tid PO), intramuscular fluphenazine (75mg/month) and biperidene (2mg/day PO). He showed a satisfactory response to treatment, and fluphenazine was withdrawn. Two weeks later, he began with verbosity, psychomotor agitation, and grandiosity delusions. Oral haloperidol was initiated (5mg/day for five days, and then 10mg/day), but he rapidly developed intense extrapyramidal symptoms. So, it was tapered until being suspended, and substituted by 4mg/day of perphenazine. Within the first five days of this switch, he showed a clinical picture characterized by verbosity, speech impairment, motor agitation, fear, hand shaking, diaphoresis and joint rigidity. The temperature was measured, and no fever was documented. It was thought to be a new extrapyramidal event, with good response to intramuscular biperiden and transient oral benzodiazepines, and perphenazine was substituted by thiothixene (10mg/day). Five days later, a similar episode appeared: malaise, fear, speech impairment, diaphoresis, tremor, muscle contractures, agitation, and hypertension. But this time some other signs and symptoms appeared: a remarkable sialorrhea, nausea, vomiting, and bronchorrhea (the patient could not rest at supine position because of the dyspnea that mucosa secretions caused him; as a matter of fact, Medical Department even considered endotracheal intubation, since oxygen saturation decreased during this bronchorrhea episode, but at the end it was not
necessary). No diarrhea was reported. The patient was asked to describe the symptoms of this crisis, and answered that muscle contractions, though present, were not the main problem, but heart beatings and hyper-production of thick saliva. It was noteworthy that he showed symptoms around 6 pm, the time pills were given. Thiothixene was substituted by 1mg/day of risperidone plus 10mg/day of diazepam, and one week after this low starting dose, cholinergic symptoms were registered again. Supporting the thesis of cholinergic rebound, risperidone dose was increased, and so was the biperiden’s. The patient reached 4mg/day of risperidone, with no more cholinergic crises, less extrapyramidal symptoms, and a satisfactory mood stabilizing response.

Manifestations of diverse receptor blockade by typical antipsychotics are common, but rebound symptoms are not always expected. The first assumption, in this case, was extrapyramidalism. In fact, it is plausible that extrapyramidal effect was the underlying cause of the symptoms within the first days of haloperidol and perphenazine. Nevertheless, clinical evolution warned about something else after perphenazine withdrawal: sialorrhea, nausea, vomiting, and bronchorrhea; signs that were not explained by the single dopaminergic antagonism. The first task was trying to gather those manifestations into a syndrome category. The patient reported two cardinal complaints: palpitations and sialorrhea. Together with the bronchorrhea and the gastrointestinal symptoms, they were consistent with a hypercholinergic environment. After that, to consider a rebound syndrome, the clinical presentation should be consistent not only with the receptor blockade profile but with the time of symptoms appearance. The crisis was five days after perphenazine withdrawal: enough time to see that effect of the drug had finished; its cholinergic antagonism had already passed.

Some pharmacological considerations should be made further to support the postulation of a cholinergic rebound. First, there were not highly anticholinergic antipsychotics (like olanzapine, or clozapine), but the cholinergic rebound is not limited to those. Furthermore, withdrawal syndromes are not exclusively due to drug’s features (even this is maybe the main element to consider), but also to idiosyncratic sensitivity (5). The antipsychotic switch that included cholinergic symptoms was from perphenazine to thiothixene. According to potencies of antipsychotic agents at neurotransmitter receptors, perphenazine has an intermediate muscarinic M1 affinity (ki= 1500nM, compared to ki >20,000 for haloperidol and ki >10,000 for thiothixene (6).

Second, it looks like the patient was very sensitive to D2 blockade unmodified by serotonin-mediated effects (in the fact that is why he showed those extrapyramidal symptoms with typical drugs). However, this only explains why he did not have extrapyramidalism with risperidone and does not explain the cholinergic symptoms. I suggest that those were caused by losing the perphenazine M1 blockade, and disappeared precisely because of the risperidone’s weak muscarinic affinity (ki >10,000), compared with perphenazine’s.

As limitations of this case report, the first would be using only one atypical antipsychotic. (Since the patient’s diagnosis and symptoms, risperidone would have been an excellent first choice. However, the institution where events happened belongs to the social security system, where we have only one atypical antipsychotic: risperidone. So, we are encouraged to start with typical). Other include the co-occurrence of extrapyramidalism; the appearance of cholinergic symptoms that could have been mistaken as extrapyramidalism (for example, the thick saliva as a result of a dry mouth from an anticholinergic effect); the concurrent administration of biperiden, just to mention a few of them.

Cholinergic symptoms cause serious pain and functional impairment, and one should be aware of them while prescribing neuroleptics. In the present case, a young man was switched from several typical antipsychotics because of side effects. Most of them were explained to occur as extrapyramidalism, by dopaminergic D2 blockade. However, after perphenazine withdrawal, motor symptoms were accompanied by sialorrhea, nausea, vomiting, and bronchorrhea. Those were compatible with the cholinergic rebound, and in fact disappeared when switching to an antipsychotic with a very weak muscarinic affinity. Perphenazine is not among the most anticholinergic antipsychotics, and here relies on the clinical importance of this case. So,
when motor symptoms appear while switching neuroleptics, one must consider the full clinical picture, and then correlate it with the pharmacologic profile of the current medication. In this way, the decision about tapering or raising the dose of antipsychotics will be easier.

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