

## Ultra-Rapid, Unexpected, and Full Remission of Manic Episode after Treatment with Haloperidol High Doses – 2 Case Reports

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### Abstract

Bipolar disorder is a psychiatric condition that can develop severe manic episodes which can be life threatening for patient or others and therefore rapid intervention is required to prevent this. Antipsychotic treatment with FGAs (first generation antipsychotics) is still frequently used for quick sedative effect as well as for the improvement of manic symptoms. Management of agitation in patients with psychiatric disorders is a major problem in acute psychiatric settings with insufficient personnel, situation which is frequent in Romania and other East European countries. FGAs (first generation antipsychotics) and BDZ (benzodiazepine), especially as intramuscular formulation, alone or in combination, have been the treatment choice for extreme agitation and aggression all over the world. Haloperidol is still used to treat schizophrenia and acute psychosis as well as agitation, extreme aggression and manic episode. It is known that common adverse effects include extrapyramidal reactions, restlessness, neuroleptic malignant syndrome, and tremor. High doses of haloperidol are administered to patients when RT (rapid tranquilization) is needed. We present two cases of unusual, unexpected, ultrafast and full remission of a manic episode after treatment with haloperidol high doses.

**Keywords:** Haloperidol; Antipsychotic; Mania; Agitation, Remission; Violent behavior; Bipolar disorder; Hospitalization

### Introduction

Bipolar disorder is a psychiatric condition that can develop severe manic episodes which can be life threatening for patient or others. Violent, uninhibited and irresponsible behavior is found in 10-13% of emergency cases or even more if there is concomitant consumption of alcohol or drugs [1,2]. Often, rapid intervention is required to prevent this. Antipsychotic treatment with FGAs (first generation antipsychotics) is still frequently used for quick sedative effect as well as the improvement of manic symptoms. Management of agitation in patients with psychiatric disorders continues to be a major problem. FGAs (first generation antipsychotics) and BDZ (benzodiazepine), especially as intramuscular formulation, alone or in combination, have been the treatment choice for agitation all over the world. RT (rapid tranquilization) is a method frequently used in acute psychiatric settings but without strong evidence base, recommendations being mainly based on clinical experience and partly on theoretical considerations [3]. Intramuscular injections with haloperidol and lorazepam have been the most widely used drugs for agitation treatment [4]. Haloperidol is the first of the butyrophenone series of major antipsychotics. The chemical designation is 4-[4-(p-chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone. It exerts efficacy mainly through the antagonism of dopamine receptors [5]. It is used frequently to treat schizophrenia and in acute psychiatric settings as well as to treat delirium and acute psychosis. Side effects including extrapyramidal reactions, dry mouth, tremor, weight gain and neuroleptic Malignant syndrome are the most common [6].

We present details of two patients with bipolar disorder in severe manic episode. The patients were treated with haloperidol high doses for a short period of time with rapid and full remission of manic symptoms without EPS (extrapyramidal side effects). Informed consents for publication have been obtained from patients and are available for editor.

### Case Report 1

We report the case of a 44 years old male admitted to the emergency room for the following symptoms: psychomotor agitation, aggression, verbose, dysphoria and grandiosity delusions. Patient's parent's

statements show that starting with 10 days prior to hospitalization, he became gradually agitated, talkative, making unrealistic business plans and more preoccupied with religion beyond what they considered normal. They became aware of an abnormal behavior when the patient affirmed that he developed a plan to save the country from bankruptcy. Two nights before admission the patient drove to Bucharest City, to meet the President of the Republic of Romania, but he crashed into a bridge. He was transported by ambulance to the emergency department of the local hospital. After tests (negative results for drug screening) and CT scan were completed the patient was released and left the hospital saying that 'he had a lot of work to do' but few hours later he was brought by relatives to the psychiatric hospital for extreme agitation and very aggressive behavior.

The history shows that the patient was diagnosed in 2010 with bipolar disorder when he was hospitalized for the first time for a manic episode with psychotic features (delusion of grandiosity) treated with haloperidol up to 10 mg/day, valproate up to 2000 mg/day and zopiclone 7.5 mg/day. After discharge he followed treatment only for one month due to lack of insight. It is reported by the parents that the patient continued to be talkative and wasteful with money. As a consequence it is reported that he lost a lot of money in Real Estate business trying to open new business, even his house. He was forced to live with his parents. The patient's father suffers from bipolar disorder with good outcome under treatment with olanzapine 10 mg/day and his mother was diagnosed with histrionic personality disorder.

After involuntary admission the patient remained extremely agitated requiring physical restraint. He was given 10 mg haloperidol and 20 mg diazepam i.m. at 8.00 pm. After 4 hours (0.00 am), the

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patient's condition was unchanged and he continued to shout and threaten the medical personnel. He was given again haloperidol 10 mg and diazepam 20 mg intramuscular. After another 4 hours (4.00 am), the patient remained highly agitated and haloperidol therefore another dose of 10 mg intramuscular was given. The patient fell asleep after 30 minutes. In the morning, when the patient woke up he remained hostile, claiming and threatening. During the day there were administered haloperidol 5 mg BID, diazepam 10 mg BID, valproate 500 mg BID and trihexifenidil 2 mg BID.

48 hours after admission the patient was calm, cooperative, without psychotic symptoms. During this period, he received haloperidol 50 mg. After 3 days of hospitalization he was evaluated by a panel of physicians. Conclusion was absence of manic symptoms with high level of insight. The patient recognized the need for treatment, the disease's symptoms and apologized for his behavior. Because the patient status permitted with CGI-BP-I score 1 (Clinical Global Impression Scale – Bipolar Improvement) [7] a CT scan was performed and the result was normal. The drug screen at admission was negative. Lab results included: glucose=86 mg/dl, urea=45 mg/dl, creatinine=1 mg/dl, Na=140.1 mmol/L, K+=3.72 mmol/l, full blood count, cholesterol=156 mg%, triglyceride 74 mg%, 31AST=31U/L, ALT=28 U/L, GGT=40 U/L, WBC=  $7.2 \times 10^3$ /uL. CK performed at 48 hours showed a value of 422 U/L. ECG was normal with sinus rhythm, heart rate was 98 BPM and QTc=437 ms. There were no extra-pyramidal side effects.

As a result, the patient was discharged after eight days with indication for treatment with first generation long acting antipsychotic zuclopentixol 200 mg injection at every two weeks. One month follow-up call revealed that patient is still in remission. After 3 months, the patient requested oral treatment (he and his family were afraid about FGA side-effects) and he was switched to quetiapine 400 mg daily with good results regarding compliance and treatment adherence.

## Case Report 2

The second case refers to a 41 years old female with the onset of bipolar disorder at the age of 26 admitted to the emergency room for psychomotor agitation, violent behavior towards her husband and neighbors, logorrhea, delusions of grandeur and delusions of persecution regarding her exceptional mental abilities. The ymrs score was 34 and cgi-bp-s was 6. The drug screen was negative. The patient's husband affirmed that she stopped medication one month ago after 3 years of good remission under treatment with quetiapine xr 300 mg daily. despite previous evidence of relapses and long hospitalization when she stopped medication she refused systematically to be appointed to her psychiatrist. The family reported that one week before admission she showed uncharacteristic behavior, starting to wear short and violently colored robes with many rings and strident make-up and became more interested in sex.

In the first day the patient required physical restraint and she was given haloperidol 10 mg and diazepam 20 mg intramuscular at 11.30 am followed 4 hours later (15.30 pm) by haloperidol 10 mg intramuscular and valproate 1000 mg oral. The patient's condition remained mainly unchanged and she continued to shout and spit. she was given again haloperidol 10 mg and diazepam 20 mg intramuscular at 8.00 pm. the treatment was maintained at the same doses on the second day and the patient's status was significantly improved. No extra-pyramidal side effects have been recorded. After 72 hours the patients status was very much improved (cgi-bp-i=2). Haloperidol treatment was tapered for 2 days and then stopped and simultaneously quetiapine xr was initiated starting with 300 mg on the first day and 600 mg daily thereafter. The

decision to introduce quetiapine was made based on the previous treatment response with less side effects. The patient was discharged after 8 days. lab results included: full blood count, glucose=95 mg/dl, urea=44 mg/dl, creatinine=1.1 mg/dl, na=144.1 mmol/l, k+=3.71 mmol/l, cholesterol=222 mg%, triglyceride 156 mg%, ast=31 u/l, alt=25 u/l, ggt=28 u/l, ck performed at 48 hours showed a value of 248 u/l. ecg was normal with and qtc=430 ms.

## Discussion

Our case reports are about two patients with bipolar disorder admitted in an acute psychiatric hospital for extreme agitation, aggression, and irritability. The particularity of reports is the unusual, unexpected, ultra-rapid and full remission of a manic episode after treatment with haloperidol up to 50 mg in 48 hours with no side effects. Despite the fact that we intended to treat agitation and violent behavior we obtained full and sustained remission in two cases of severe manic episode. In both cases the intramuscular formulation of lorazepam was not available at site. The personnel were insufficient in the night shift and the risk of aggression towards medical staff and patients was extremely high. The patients were well known in the hospital for their severe relapses and were treated in the past years by at least two different psychiatrists for Bipolar Disorder.

The management of aggressive and violent manic patients often includes SRU (seclusion or physical restraint) and medication [7,8]. SRU is a highly stigmatizing method with significant risk for serious incidents [9]. Drugs with rapid tranquilizing or sedating effect without producing distressing or dangerous adverse effects are desirable. Haloperidol is a highly potent neuroleptic with a low price, used when tranquilization is needed. It is widely available and is used in emergency situations alone or/and in combination with benzodiazepines. As an exponent of FGA it has been the standard of care for acute agitated patients in emergency room settings for decades especially for aggressive or uncooperative patients [10,11]. Lorazepam is used for treatment of agitation and it is available as an intramuscular formulation [12]. Second generation antipsychotics such as olanzapine and risperidone seem to have the best profile of antimanic action [13]. In a recent study published in *Lancet* in 2013, haloperidol is considered in top 4 ranking of antimanic drugs [14]. Many studies show atypical antipsychotics as effective as FGA in treatment of agitation but with significant low incidence of extrapyramidal side effects, including akathisia, dystonia or tardive dyskinesia [15]. There are intramuscular formulations of SGA for olanzapine, ziprasidone and aripiprazol. Of the atypical agents, olanzapine [16] and aripiprazol [17] are at least as effective as haloperidol at producing rapid tranquilization in acutely agitated patients. This medication is largely unavailable in public hospitals in many countries because the price is still expensive.

Clozapine is demonstrated to be efficient and safe for patients with treatment-resistant bipolar disorder [18] but often is almost impossible to be administered in severe agitated patients especially when they refuse oral medication. In these cases only intramuscular medication can be used.

Despite the previous reports of RT effect of haloperidol in schizophrenia, acute psychosis and manic episode [19] our report seems to be the first highlighting the unusual rapid and full remission of manic episode in patients treated with high doses of haloperidol for 48 hours.

## Conclusions

Haloperidol remains a good option in terms of rapid action and

safety. It is still largely utilized in emergency psychiatric settings for rapid tranquilization. Our results showed the rapid anti-manic effects when haloperidol is used in high doses for a short period. Further studies may lead to this type of action instead of leaving patients exposed to longer periods of aggression with frequent physical restraint actions.

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