CASE REPORT

Modafinil in schizophrenia: is the risk worth taking?

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SUMMARY

Schizophrenia is a severe mental disorder characterised by positive and negative symptoms. Negative symptoms are difficult to treat and there is no specific treatment. In small trials, modafinil has been studied in association with antipsychotic treatment. We present three cases of its use; two have developed positive symptoms and one developed renal impairment. Further studies are needed to assess its usefulness in schizophrenia and safety in this group of patients.

BACKGROUND

Schizophrenia is a severe mental disorder characterised by positive and negative symptoms. Cognition has been a hallmark of this disorder, well described by Kraepelin denomination of *Dementia praecox*.¹ The cognition deficit of schizophrenia is a major field of study, but efficacious treatment is still far away from clinical practice. Cognitive deficits are related to functional outcome, and for a long time several pharmacological treatments have been tested, most of them with negative results.²

Cognition depends on the balance of several neurotransmitters, but many studies point dopamine as one of the main players.³ However, dopamine has a delicate balance. When dopamine is in excess in the striatum, psychosis develops. When it is insufficient in the prefrontal cortex, negative and cognitive deficits prevail.⁴

Negative symptom is a category for several types of symptoms (alogia, anhedonia, asociality, avolia and blunted affect).⁵ It is hypothesised that these symptoms are related to hypofunction of the prefrontal cortex and other subcortical structures related to the limbic system.⁶ Augmenting dopamine and serotonin transmission was shown to augment limbic and cortical activity.⁷

In small trials, modafinil has been studied with the expectation of improving negative symptoms and cognitive deficits.⁸ The biological rationale for using this class of drugs is that it increases the levels of several neurotransmitters (eg, dopamine, glutamate, serotonin) and reduces the levels of γ -aminobutyric acid, resulting in more neuronal activation.⁷

Our aim was to assess if modafinil as an add-on drug could reduce refractory negative symptoms.

CASE PRESENTATION

We present three cases of the use of modafinil in patients with stable schizophrenia, with more than 4 years without psychotic symptoms, treated with

an antipsychotic for more than a year and with significant negative symptoms.

Case 1

A 55-year-old man has been followed in our department for more than 10 years.

With the first hospital admission in our department, 10 years ago, he was diagnosed with schizophrenia according to the criteria established by the International Statistical Classification of Diseases and Related Health Problems 10th Edition (ICD-10), with a history compatible with the disease from his 30s.⁹ The cultural aspects of his ethnic group (Cap-Vert) are relevant for the delay in initiating treatment from the healthcare sector, as psychosis is often seen first as a spiritual phenomenon.

He is a smoker and has a medical history of essential arterial hypertension and high cholesterol.

He had mainly negative symptoms, being without psychotic symptoms for 9 years:

- ▶ limited speech, having small conversations with his partner
- ▶ blunt affect
- ▶ limited social relations with his family, without actively initiating them
- ▶ no physical activity, limited to small works in a small garden near the house
- ▶ no sexual interest.

His previous medication before the trial with modafinil was risperidone 2 mg once a day, sertraline 50 mg once a day, indapamide 1.5 mg once a day, perindopril 8 mg once a day and salicylic acid 100 mg once a day.

These symptoms maintained even after changing the medication to the lowest dose possible and with adjunctive selective serotonin reuptake inhibitor (SSRI).

Case 2

A 44-year-old man has been followed in our department for more than 10 years.

He has been diagnosed with schizophrenia since his 20s according to the criteria established by the ICD-10. He had four admissions, the last of which was 4 years ago. Since then, depressive symptoms have appeared and were treated with venlafaxine. In the last 3 years, the patient has been clinically stable. He has the comorbidity of alcohol dependence, in abstinence for the last 5 years. He additionally has a relevant history of controlled HIV infection (CD4⁺ Th cells >500 cells/mm³) without complications. He has been taking emtricitabine, rilpivirine and tenofovir disoproxil in the last 5 years.

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During follow-up, the patient manifested mainly negative symptoms, being without psychotic symptoms in the last 4 years:

- ▶ limited speech, having small conversations with his family
- ▶ blunt affect, reporting being absent of depressive cognitions
- ▶ limited social relations with his family
- ▶ no physical activity, not even helping his family at home
- ▶ no sexual interest.

His medication before the trial of modafinil was monthly zuclopenthixol decanoate 100 mg, amisulpride 200 mg twice a day, quetiapine 300 mg once a day and venlafaxine 75 mg (long-acting formulation) once a day.

These symptoms maintained even after changing the medication to the lowest dose possible and with adjunctive antidepressant. The antipsychotic dose was reduced to a minimum because of side effects and the patient remains asymptomatic. A long-acting injectable was maintained because of past non-adherence and the choice was zuclopenthixol because of its side-effect profile, previous response and cost.

The patient had a refractory insomnia and has previously been taking cyamemazine. This drug was changed to quetiapine (which has a better cognitive and side effect profile).

Case 3

A 65-year-old man has been followed in our department for more than 10 years. He has been diagnosed with schizophrenia since his 20s according to the criteria established by the ICD-10, with a family history of an aunt with schizophrenia and a father with Alzheimer disease. An MRI was done 2 years ago without major findings.

He had mainly negative symptoms, being without psychotic symptoms for more than 10 years:

- ▶ very limited speech, answering only one word occasionally and without spontaneous speech;
- ▶ blunt affect
- ▶ without social relations, even with family. He would prefer to stay laid in bed than meeting his children;
- ▶ slow movements and without any signs of motivation;
- ▶ no sexual interest.

Before the trial with modafinil, his medication was clozapine 100 mg, a monthly injection of aripiprazole 400 mg, venlafaxine 150 mg (long-acting formulation) once a day and trazodone 300 mg (long-acting formulation) once a day.

The symptoms maintained even after adjusting antipsychotic medication to the minimal effective dose to avoid secondary causes of negative symptoms. Before the modafinil trial, two antidepressant drugs were tested as add-on. The first antidepressant was sertraline titrated up to 100 mg once a day. The second was venlafaxine. Trazodone was used to treat refractory insomnia. Because of previous non-adherence and an episode of aggression, aripiprazole was used in association to clozapine.

TREATMENT

We started the medication in our Community Mental Health Team with a multidisciplinary intervention and family support in 2016. Patients and family members accepted the trial and were informed of the risks, being told to contact the team if any symptom developed. The three cases started with 100 mg of modafinil and more frequent follow-up appointments were scheduled. We started modafinil in this low dose as it is the recommended starting dose in Portugal for the approved uses.

OUTCOME AND FOLLOW-UP

Case 1

The patient after 6 weeks of treatment developed persecutory delusional ideation, believing that his family was in danger because of the neighbours. These symptoms were not seen as relevant by the family and the patient got worst needing to be admitted to the psychiatric inpatient unit. Modafinil was stopped, and after 2 months the positive symptoms remitted, maintaining the same negative symptoms.

Case 2

The patient after 2 months of treatment developed command hallucinations and committed a suicide attempt with bleach. He was admitted to the gastroenterological department and proper care was administered. He recovered without significant morbidity and is stable without depressive or psychotic symptoms. The negative symptoms are present as before.

Case 3

After taking modafinil for 3 weeks, the patient developed an acute renal impairment and was hospitalised. No infectious agent was identified and no other aetiology was found. He had a reduction of 58 mL/min in estimated glomerular filtration rate (baseline creatinine of 1.2 mg/dL, increased to 3.3 mg/dL and reduced to 1.4 mg/dL 2 months after).¹⁰ The wife was alarmed with this situation and refused to maintain the treatment. The patient did not change his psychiatric symptoms during the trial.

DISCUSSION

Modafinil has shown conflicting results in the trials developed so far. In terms of negative symptoms, good results were seen in four trials, adjunctive to antipsychotic medication in patients with stable schizophrenia.^{11–14} Negative results were seen in several trials.^{15–18} One trial found self-subjective improvements but no objectively measured improvement was found.¹⁹

Regarding cognitive deficits, positive trials showed improvement in short-term verbal memory and spatial planning task.²⁰ One trial that used modafinil as adjunctive to cognitive training showed benefit in both groups, without significant difference.²¹ Some trials showed no influence in cognition, but with improvement in social cognition — recognition of sad facial expressions.⁷ But there are also negative results in some trials, showing no significant difference from placebo.^{7, 18} In neuroimaging studies, modafinil showed an increased activation of the anterior cingulate cortex and dorsolateral prefrontal cortex.^{22, 23}

Regarding motor symptoms, one trial showed an improvement in motor side effects.²⁴ Another trial showed an increase in general motor activity measured by an accelerometer.²⁵

Regarding worsening of psychotic symptoms, one study showed that 5% of patients developed symptoms of psychosis and in another 18%.^{14, 25} We found two case reports in the literature worth mentioning. One is the case of a patient taking only 100 mg of modafinil who developed psychosis, without psychiatric history.²⁶ The second is a patient with history of psychosis whose symptoms recurred when modafinil 200 mg was added to quetiapine 600 mg.²⁷ Our patients were without psychotic symptoms for at least 1 year and were tested only with the low dose of 100 mg and still developed major psychosis.

Regarding the renal impairment, only one case is described in the literature and is related to the introduction of armodafinil to the treatment of excessive daytime sleepiness associated

with sleep apnoea. The patient developed acute interstitial nephritis, which recovered after suspension of the drug, and the authors assumed a probable relation with its introduction.²⁸

This group of patients has chronic stable schizophrenia and supposedly is less prone to improvement. For this reason, they should be in a lower risk to develop positive symptoms; in patients 1 and 2, we can argue that their effective low-dose treatment could be a reason for them developing positive symptoms with modafinil.

Higher doses of antipsychotics could protect patients from these side effects, but would worsen the negative symptoms.

Future research should compare the reduction of antipsychotics to the minimum versus maintaining the dose and adding a stimulant like modafinil.

Learning points

- ▶ Modafinil in schizophrenia has some important risks, and further trials should monitor closer psychotic and general medical symptoms of these patients.
- ▶ Modafinil may worsen the positive symptoms of schizophrenia in some patients.
- ▶ Probably the risk and benefit are different in terms of different antipsychotics and dose chosen.
- ▶ The risk of psychosis should be very carefully assessed if a patient with schizophrenia initiates a trial with modafinil.

Contributors DN and JG were responsible for planning, conduct, reporting, conception and design. CS was responsible for reporting.

Competing interests None declared.

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