CASE REPORT

Add-on oral olanzapine worsens hallucinations in schizoaffective disorder

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SUMMARY

Anecdotal evidence tends to favour olanzapine in the treatment of hallucinations in patients with schizophrenia spectrum disorders; however, no conclusive evidence is available on this topic. We report here a clinical case in which a 46-year-old man, suffering from a schizoaffective disorder (depressed type), underwent olanzapine treatment (20 mg/day). After inducing an initial amelioration, the patient had a re-exacerbation of auditory hallucinations and a clinical and psychosocial worsening, which subsided after olanzapine discontinuation. Olanzapine may induce a worsening of hallucinations in a psychotic disorder with substantial affective component and therefore its use should be carefully evaluated in such cases.

BACKGROUND

Hallucinations still represent a key feature of several neurological and psychiatric syndromes,¹ and the mainstay of their treatment is represented by antipsychotic drugs.² Second generation antipsychotics (SGAs) have been reported to have a beneficial effect on hallucinations,^{3,4} with lower risk of extrapyramidal side effects and a positive impact on social and cognitive functioning,⁵ with respect to first-generation antipsychotics. Among SGAs, olanzapine, amisulpride, ziprasidone and quetiapine have shown equal efficacy in treating hallucinations.²

However, anecdotal evidence tends to favour olanzapine treatment of hallucinations in psychotic disorders, based on its higher efficacy in treating misperceptions, its positive impact on negative, motor and mood symptoms, and its lower rates of early therapy discontinuation, with respect to other SGAs.^{6,7} When psychotic and affective symptoms are both present, the treatment with olanzapine has been suggested as the first therapeutic choice.⁸

However, to date, no specific and consistent evidence on how to treat prominent hallucinations in schizoaffective disorders exists.⁹ This leaves a substantial gap of knowledge on the topic, and evidence concerning the efficacy and tolerability of olanzapine in the treatment of prominent hallucinations within schizoaffective disorders is still greatly needed.

We report here the clinical case of a patient affected by schizoaffective disorder who, after an olanzapine add-on, had a worsening of hallucinations.

CASE PRESENTATION

A 46-year-old married man presented almost 10 years ago with persecutory delusions of being drugged/poisoned by workmates, auditory

hallucinations (mood-congruent commenting voices with hostile tones) and depressive episodes, and received a Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV diagnosis of schizoaffective disorder (depressed type).

He was treated for several years with first generation antipsychotics (haloperidol and trifluoperazine, both at therapeutic doses) as well as with several antidepressants (clomipramine, paroxetine and duloxetine), reporting only occasional ameliorations, usually followed by a worsening of the clinical picture, with a clear tendency to chronic course and significant social and occupational dysfunction. At the time of our first observation, he was treated with zuclopentixole (30 mg/day), valproate (800 mg/day) and duloxetine (60 mg/day), which rapidly induced an amelioration of the clinical picture.

However, after a year of symptoms' stabilisation and on request of the patient, the pharmacological therapy was gradually tapered and then discontinued, leaving only 400 mg/day of valproate (to control occasional impulsivity and prevent the risk of mood swings).

Within a few months, due to worsening of family relationships, the patient presented a prominent recrudescence of hallucinations: the patient had visual (erotic scenes with his mother) and somatic (I feel vibrations all over my body) hallucinations, which induced complete social withdrawal, with the areas of work, interpersonal relations and self-care markedly below the functioning level achieved before. At the time of his admission to our inpatient unit (week 1), he was also severely depressed, with prevailing aspects of depressed mood for almost the whole day, every day, anhedonia and lack of will and interests, slow thinking, poor concentration, poor memory, low energy and lack of interest in life (table 1).

In order to control hallucinations, olanzapine was gradually introduced, and within 2 weeks, a daily dose of 20 mg was reached. This induced an amelioration of misperceptions and the patient was discharged when a significant improvement of his clinical symptoms (persecutory delusions faded, mood was close to euthymia) was observed. One week after hospital discharge, he reported normal social, work and family functioning (week 4). During hospitalisation, adherence to treatment was carefully checked by the nursery staff (while after discharge, it was assured by his wife). Olanzapine plasma level at week 3 was 270 ng/mL (normal range value: 1.2–208.0 ng/mL¹⁰; however, steady state levels in men have been reported to be

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Table 1 Psychopathological and functioning indices

	Before olanzapine treatment (week 1)	Olanzapine treatment (week 4)	Olanzapine treatment (week 6)	After olanzapine discontinuation (week 9)
PANSS (TOT)	61	39	68	33
PANSS (POS)	20	11	25	8
PANSS (NEG)	8	8	8	8
PANSS (GP)	33	20	35	17
PANSS (HAL)	5	3	6	1
PSYRATS (DS)	26	18	36	0
PSYRATS (AH)	15	10	15	1
CGI (SI)	4	1	6	1
CGI (GI)	0	2	0	1
GAF (TOT)	50	60	40	80

AH, hallucinations; CGI, Clinical Global Impression (19); DS, delusions; GAF, Global Assessment of Functioning (APA, DSM-IV TR); GI, global improvement; GP, general psychopathology scale score; NEG, negative scale score; PANSS, Positive and Negative Syndrome Scale (17); POS, positive scale score; PSYRATS, Psychotic Symptoms Rating Scales (18); SI, severity of illness; TOT, total score.

127±47 ng/mL, after 8 weeks of treatment with olanzapine at high doses, such as 50 mg/day¹¹).

After 3 weeks of olanzapine treatment, he reported recurrent auditory, visual and somatic hallucinations, with associated social and work withdrawal, and depressed mood (week 6). He also suffered from early morning awakenings, fatigue, poor concentration and anhedonia. He had passive death wishes, as well.

DIFFERENTIAL DIAGNOSIS

In light of possible interactions between olanzapine, valproic acid and smoking, we calculated the Drug Interaction Probability Scale (DIPS¹²) score, which resulted to be 2 (ie, possible interaction).

In order to systematically estimate the probability that olanzapine induced a worsening of hallucinations, beyond simple clinical judgement, the ADR Probability Scale¹³ was used: the total ADR score of 7 of 10 confirmed that olanzapine treatment caused the observed exacerbation of misperceptions.

OUTCOME AND FOLLOW-UP

The patient was readmitted to our inpatient unit and olanzapine was discontinued. The patient reported a gradual but significant improvement in his clinical status, with total disappearance of misperceptions, after the complete suspension of the drug (week 9). After the drug had been stopped, a placebo was given to the patient for 3 days, without influencing the amelioration of the clinical status. One week after discontinuation, the olanzapine plasma level was 35 ng/mL. The patient was started on zuclopentixole (20 mg/day) and is currently being followed up. To date, there have been no psychotic recurrences and his socio-occupational functioning is back to normal (table 1).

DISCUSSION

In order to conclude that olanzapine induced a worsening of hallucinations in our case, possible confounding factors have to be further excluded. Smoking (our patient was smoking more than 30 cigarettes/day and this represents a well-known cause of lowering olanzapine plasma levels¹¹) and concurrent use of valproic acid could have decreased olanzapine plasma levels (due to metabolic interactions at the level of P-450 microsomal hepatic enzyme system¹⁴). However, several recent studies did not confirm that valproic acid significantly affects plasma concentrations of olanzapine, as only minimal decreases in the mean plasma olanzapine concentrations were reported and no

clinical psychopathological worsening was observed in treated patients.^{15–17} In fact, although our patient continued to smoke, olanzapine plasma levels after 3 weeks of co-treatment with valproic acid were in the upper high end of normal levels.^{10 11} Therefore, the lowering effect of smoking and concurrent treatment with valproic acid can both be excluded as factors involved in the loss of olanzapine's therapeutic effect. Age has also been reported to influence olanzapine plasma levels, with an average increase of 9.4% per decade of life¹⁸; our patient was in his fourth decade and, therefore, no great influence of age on olanzapine metabolism could be suspected. Moreover, genetic variations in CYP3A43, which is mainly involved in olanzapine metabolism, could explain the variability in pharmacokinetics of this SGA and, in turn, in the patient's clinical response.¹⁹

In conclusion, we advise that olanzapine may lose its therapeutic effect over time and worsen hallucinations in patients with schizophrenia spectrum disorders, with a substantial affective component.

Learning points

- ▶ There is small consensus on pharmacological treatment of hallucinations.
- ▶ Olanzapine has been reported as a preferable treatment option for misperceptions.
- ▶ Previous studies on this matter are anecdotal and our report does not confirm this evidence.

Competing interests None.

Patient consent Obtained.

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