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CASE REPORT

Trazodone and exacerbation of psychotic symptoms: an unfamiliar link

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Objective. In this case report we attempt to emphasize the unfamiliar link between trazodone and relapse of psychotic symptoms.

Method. Case report and literature review of relevant papers.

Results. We report a case of a 78-year-old woman with an established diagnosis of paranoid schizophrenia who has experienced an exacerbation of positive psychotic symptoms following initiation of 50 mg dailydose of trazodone. We noted that psychotic symptoms abated following discontinuation of trazodone.

Conclusion. Trazodone use in patients in remission from schizophrenia may be associated with relapse of psychotic symptoms and caution is required.

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Key words: Psychotic disorders, recurrence, schizophrenia, sleep initiation and maintenance disorders, trazodone.

Introduction

Trazodone's mechanism of action is quite distinctive. It is a serotonin antagonist and, at the same time, a serotonin reuptake inhibitor (Feighner & Boyer, 1988). Hence, trazodone possesses an exceptional therapeutic flexibility and is, therefore, recommended for treatment of a wide range of psychological and biological symptoms of depressive and anxiety disorders (Stahl, 2009; Taylor *et al.* 2012). Trazodone is associated with several well-documented cardiac, neurological, hepatic, sexual and hematological adverse effects (The Joint Formulary Committee, 2014). According to the trazodone drug information sheet; 'Administration of antidepressants in patients with schizophrenia or other psychotic disorders may result in a possible exacerbation of psychotic symptoms' (Summary of Product Characteristics, 2013). In this case report we attempt to emphasize the unfamiliar link between trazodone and exacerbation of psychotic symptoms in a patient with a diagnosis of schizophrenia. We, also, aim to raise the awareness of practicing clinicians to this unusual but important association.

Case report

A 78-year-old white Irish woman with an established diagnosis of paranoid schizophrenia for the last 35 years attained significant remission for a period of almost a year. She continued, even during periods of remission, to have an encapsulated fixed system of delusions that a deceased ex-partner is still alive and resides in the flat on top of hers. These psychotic phenomena were not of any distress to the patient, and she displayed reasonable social functioning during the remission period. She was compliant with zopiclone 7.5 mg and olanzapine 5 mg daily, together with monthly flupentixol 20 mg intra-muscular depot.

Sleep was noted to become quite fragmented over a week period despite taking the short acting hypnotic zopiclone. She did not sleep at all for a number of nights and, consequently, her anxiety and distress escalated with no overt exacerbation of psychotic symptoms. Remarkable anergia and exhaustion during the day time was caused by lack of night-time rest. She was not motivated to collect her medications from the near-by pharmacy or to socialize with her sisters as she used to. Sleep hygiene measures proved ineffective. An increase in the dose of olanzapine was not a prudent option for two reasons. First, she was recently diagnosed with early stage Parkinsonism (for which no pharmacological intervention was initiated), a disorder which olanzapine can exacerbate significantly (Graham *et al*. 1998; Fernandez *et al.* 2003). Second, according to her past psychiatric history, a clearly documented increased risk of falls was noted on previous higher doses of olanzapine. Physical examination and biochemical investigations were unremarkable. She was cognitively intact despite her age. She has been taking zopiclone for a number of months. Given that it became ineffective, it was discontinued.

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A trial of trazodone at the dose of 50 mg was commenced for hypnotic effect. Improvement in terms of sleep hours and morning energy levels was remarkable over a period of just 2 days. She communicated satisfaction with the sleep-inducing effect of trazodone and was observed to be more relaxed and calm.

Remission in terms of sleep continued to take place on the daily 50 mg dose of trazodone. However, 2 weeks later, her psychotic symptoms deteriorated. She displayed evidence of delusions of thought interference and persecutory delusions, all with content related directly to her ex-partner. She reported a delusional belief that he came back to 'torment' her. She asserted that he was aware of all her activities as he was capable of accessing and controlling her thoughts. She has also developed auditory hallucinations. She heard her ex-partner 'skulking' around in the top flat. She shouted out loud telling him to go away, but she heard him laugh at her. She firmly believed that he was following her everywhere and playing 'mind games'. These experiences adversely affected her (recently restored) sleep structure and her worries caused considerable initial insomnia with marked sleep latency. Trazodone was discontinued and replaced with flurazepam 15 mg dose. Sleep improved substantially and psychotic symptoms dissipated in 2 days following cessation of trazodone. She declared that her ex-partner ceased to hassle her. She described him as 'just a thought in her mind'. She was no longer anxious or concerned by him.

Discussion

A number of case reports documented an association between trazodone and development of psychotic symptoms (Kraft, 1983; Patterson & Srisopark, 1989; Mizoguchi & Monji, 2005). Our finding is consistent with these case reports. However, a remarkable body of evidence suggest safety for trazodone use in psychotic patients, especially the elderly (Sultzer *et al.* 1997). We observed exacerbation of psychotic symptoms immediately following administration of trazodone and the resolution of such symptoms following trazodone discontinuation. A remarkable temporality was noticed between the exacerbation of psychotic symptoms in this patient and trazodone treatment. In a case reported by Mizoguchi & Monji (2005), psychotic symptoms subsided following termination of trazodone treatment and adding haloperidol. A unique occurrence in our patient is that resolution of delusional and hallucinatory experiences was achieved exclusively by stopping trazodone. Increasing the dose of olanzapine (which the patient was already taking) or adding in another antipsychotic medication was unnecessary.

It is arguable that the relapse our patient sustained in the course of paranoid schizophrenia is unrelated to the commencement of trazodone. However, a number of indicators point towards the contrary of such assumption. First of all, the patient was almost in remission for a year before the commencement of trazodone. There were no notable psychotic symptoms following the initial stages of sleep disturbance. In fact, after trazodone was commenced, the sleep was restored, but the psychotic symptoms worsened. Second, commencement of trazodone clearly and immediately preceded the exacerbation of psychotic symptoms. Third, withdrawal of trazodone led to full resolution of the florid psychotic symptoms. These indicators, collectively, leave little room to doubt that trazodone contributed significantly to the psychotic relapse experienced by the patient. The argument for trazodone to have exacerbated the psychotic symptoms is further supported when the pharmacological plausibility is taken into account. Trazodone, at doses of 50 mg daily, is well-known to inhibit the serotonin transporter, resulting in agonism at 5-HT_{2A} and 5-HT_{2C} serotonin receptors, rather than antagonism (Feighner, 1999). The resultant enhancement in subcortical serotonergic function may be responsible for the development of the psychotic symptoms exhibited by the patient following a 50 mg dose of trazodone (Breier, 1995; Geyer & Vollenweider, 2008).

Another unique point in this case report is the exacerbation of psychotic symptoms in a patient with an established diagnosis of schizophrenia following trazodone treatment. None of the previously published case reports (Kraft, 1983; Patterson & Srisopark, 1989; Mizoguchi & Monji, 2005) described a patient who did have a diagnosis of psychotic disorder before the commencement of trazodone.

Trazodone is primarily prescribed for treatment of depressive disorders, but was shown to be effective as a treatment for distressing insomnia in a variety of clinical settings (Karam-Hage & Brower, 2003; Bertschy *et al.* 2005). A MEDLINE systematic review carried out in 2003 reported lack of significant evidence to support trazodone's efficacy in treatment of primary insomnia (Mendelson, 2005). However, a chain of more recent studies (Thase, 2003; Bon, 2005; Wichniak *et al.* 2007; Zavesicka *et al.* 2008; Sheehan *et al.* 2009; Gałecki *et al.* 2010) corroborated some evidence to the opposite. These studies provided evidence to the speed and safety of trazodone in managing primary insomnia. Trazodone is classified as an antidepressant with sedative properties in the British National Formulary (The Joint Formulary Committee, 2014). In this case report a significant hypnotic response was noted subsequent to trazodone treatment.

Conclusion

Trazodone use in patients in remission from schizophrenia may be associated with relapse of psychotic symptoms and caution is required. Prescribing

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trazodone for treatment of primary insomnia has somewhat a conflicting evidence base and, unless strongly indicated, is better avoided, especially in patients with a diagnosis of schizophrenia or any psychotic disorder.

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Conflicts of Interest

None.

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