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Case review

SELECTIVE SEROTONIN REUPTAKE INHIBITORS-INDUCED DELIRIUM: A CASE REVIEW

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SUMMARY

***Background**: Many commonly used medications are associated with causing delirium, especially those with notable direct effects on the brain. Selective serotonin reuptake inhibitors (SSRIs) are probably the most often prescribed antidepressants and are known for their favourable side-effect profile.*

***Methods**: Medline and Toxline databases were searched for case reports of delirium caused by SSRIs. Twelve cases were reviewed in addition to our case of escitalopram-induced delirium in old age.*

***Results**: Only five cases of delirium due to SSRIs as the main or most probable etiologic factor were published in the last two decades. In two cases SSRI seems a possible additional cause of delirium in combination with other psychotropic medication.*

***Conclusions**: Although SSRIs are considered safe, they can still cause delirium in an ageing patient even when SSRI was previously used without considerable side effects.*

***Key words:** SSRI - serotonin agents – delirium - adverse effects*

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INTRODUCTION

Delirium is characterized by impairment of consciousness and attention, by global disturbance of cognition, psychomotor disturbances, disturbances of the sleep-wake cycle, and emotional disturbances (World Health Organization 1992). Partially due to its heterogeneous nature, delirium is frequently underdiagnosed in clinical practice. The psychiatric differential diagnosis of delirium is broad, as the patient may appear depressed, anxious, agitated, psychotic, or primarily cognitively impaired. Therefore it can be difficult to differentiate between delirium, other drug side effects and psychiatric symptoms and signs (Mihanović et al. 2009).

In elucidating the etiology of delirium it is helpful to consider baseline vulnerabilities as well as acute predisposing factors., Preexisting brain disease with a diminished cerebral cognitive reserve is the most important of baseline vulnerabilities to delirium. However, age-related changes of brain and body physiology including alterations in pharmacokinetics and pharmacodynamics also increase the risk of delirium (Davis et al. 2012). Several other acute brain and systemic diseases as well as medications used, especially in case of polipharmacy, are common triggers for development of delirum.

Many commonly used medications are associated with delirium, especially those with notable direct effects on cholinergic, dopaminergic, and gama-aminobutyric acid (GABA)-ergic neurotransmitter action of the brain (Bourgeois & Seritan 2006).

METHODS

Medline and Toxline databases were searched using terms “delirium” and “SSRI”, “citalopram”, “escitalopram”, “fluoxetine”, “fluvoxamine”, “paroxetine”, and “sertraline”. Case reports were selected and reviewed among articles which fulfilled these criteria and were published before 1st December 2013. Our case is also described and included in this review.

RESULTS

Eight published reports with twelve cases of SSRI induced delirium were found while searching through Medline and Toxline databases. Our case is also included in this review (Table 1).

Case report

A single man first noticed periods of melancholy, insomnia, and reduced communicativeness in puberty. By nature a quiet and sensitive man, he occasionally became more active and sociable. Periods of more pronounced mood changes developed in middle age. He went to sleep feeling well and woke up hypobulic and physically drained. Despite treatment with amitryptiline and thioridazine, he remained depressed and worried. Later he suddenly became hypomanic, irascible, logorrheic, he began planning many projects, overestimated his abilities and resigned from his job. He was initially prescribed haloperidol and thioridazine and continued treatment at the outpatient clinic.

† Ales Kogoj has died on July 2, 2014

Table 1. Case reports of SSRI-induced delirium

Reference	Patient	Medication (daily dosage)	Symptoms	Comment
Kogoj	male, 86 years, bipolar disorder	escitalopram 10 mg, clomethiazole 400 mg, hydroxyurea 1000 mg bid, acetylsalicilic acid 100 mg, digoxin 0,1 mg, carvedilol 3 mg, pantoprazole 20 mg, iron (iii)-hydroxide 200 mg	disorientation, visual and olfactory hallucinations, anxiety, psychomotor hyperactivity	escitalopram probable etiologic factor
Delić & Pregelj 2012	male, 65 years, psychotically depressed	citalopram 20 mg i.v.	physically aggressive with psychomotor hyperactivity, disorientation and urinary incontinence	i.v. citalopram the main etiologic factor
Chistyakova & Amos 2008	female, 35 years, depression	fluoxetine 40 mg, lamotrigine 400 mg	confusion associated with visual and auditory hallucinations	lamotrigine the main etiologic factor (receiving fluoxetine for five years)
Chan et al. 2006	male, 51 years, depression	bupropion SR 150 mg, fluoxetine 40 mg, bromazepam 3 mg, and alprazolam 1 mg	disorientation to time and place, impairment of attention and memory, fluctuations of awareness to the surroundings, auditory and visual hallucinations	bupropion the main etiologic factor (receiving fluoxetine for more than one month)
Amir et al. 1997	female, 71 years, bipolar disorder type 2	fluoxetine 20 mg, trazodon 100 mg	agitation, confusion, hyperreflexia, nausea, vomiting, diaphoresis, fever, elevated blood pressure, tachycardia, general tonic clonic seizure	possible serotonergic syndrome
Paul & Bhtara 1997	female, 50 years, depression	protriptyline 10 mg, fluoxetine 20 mg	auditory, visual, and olfactory hallucinations	fluoxetine possible etiologic factor (in combination with protriptyline)
Byerly et al. 1996	female, 26 years, depression with psychotic features	sertraline 200 mg, haloperidol 9 mg daily, lithium 900 mg daily, benztropine 5 mg daily	disorientation to time, visual hallucinations, disorganized speech and an ataxic gait, mydriasis, dry/warm skin, hypoactive bowel sounds and marked dry mouth	benztropine the main etiologic factor (sertraline, lithium and risperidone restarted without delirium)
Roth et al. 1994	female, 57 years, recurrent psychotic episodes	fluoxetine 60 mg, perphenazine 12 mg, benztropine 3 mg, lithium 600 mg, clonazepam 2 mg	increasingly confused, difficulty concentrating, distracted, poor immediate recall, hallucinations, delusions	fluoxetine possible etiologic factor (fluoxetine reduced from 60 to 20 mg)
Roth et al. 1994	female, 55 years, schizoaffective disorder	fluoxetine 20 mg, benztropine 1 mg, haloperidol 2 mg, lithium 600 mg	disorientation, confusion, poor memory and attention, sleep disturbance, ataxia	fluoxetine probable etiologic factor
Roth et al. 1994	male, 70 years, depression with psychotic features	paroxetine 10 mg, perphenazine 24 mg, benztropine 1,5 mg	disorientation, agitation, visual hallucinations	benztropine the main etiologic factor (restarted paroxetine 20 mg without delirium)
Roth et al. 1994	male, 79 years, bipolar disorder	fluoxetine 40 mg, benztropine 1,5 mg	drowsiness, diaphoresis, restlessness, mild euphoria, tremor, ataxia, myoclonus,	benztropine the main etiologic factor (fluoxetine and perphenazine restarted without delirium)
Roth et al. 1994	female, 47 years, depression, auditory hallucinations	paroxetine 20 mg, perphenazine 16 mg, benztropine 2 mg	disoriented, confused, impaired short-term memory	paroxetine probable etiologic factor (perphenazine and benztropine resumed)
Leinonen et al. 1993	female, 69 years, depression	fluoxetine	increased alertness, interruption of the normal sleep-wake cycle, delusional symptoms	fluoxetine the main etiologic factor

At the age of 51 he was summoned to the court of justice because of a business he had made before. After that he was admitted to the psychiatric hospital for the first time. On admission he was depressed, concerned about his financial situation, but not suicidal. In the following years he was hospitalized repeatedly. At 61 years of age he attempted suicide with injection of gasoline, twelve years later he was thwarted in an attempt to jump from height. He was treated with different antidepressants, antipsychotics, mood

stabilizers and benzodiazepines for his bipolar disorder. On several occasions citalopram up to 60 mg daily was used among other medications. The last time this was used in addition to carbamazepine 800 mg bid, lamotrigine 400 mg bid, olanzapine 10 mg, mianserin 30 mg, midazolam 7.5 mg, omeprazole 20 mg, and ticlopidine 250 mg daily was when he was 81 years old.

Computer tomography scan of the cerebrum which was performed at the age of 82, revealed chronic vascular leucopathy without any signs of fresh cerebrovascular insult. Two years later he survived acute myocardial infarction and was diagnosed with left-sided heart failure, atrial fibrillation, and gastroesophageal reflux disease.

Myeloproliferative disease with thrombocytosis ($892x10^9$/L) was diagnosed at the age of 85. Soon after that hydroxyurea 1000 mg bid was prescribed and thrombocyte levels normalized. Seven months later he became increasingly verbally aggressive and offensive, therefore higher doses of psychotropic drugs were prescribed: quetiapine 500 mg daily, lamotrigine 200 mg bid, valproic acid 1000 mg bid in addition to acetylsalicilic acid 100 mg, digoxin 0.1 mg, carvedilol 3 mg, and pantoprazole 20 mg. In spite of that, he remained noisy during the day, while at night he was restless, sleepless and he urinated on the bedroom floor. All psychotropic medication was discontinued due to suspected delirium. After discontinuation of psychotropic medication he was much more peaceful, his behaviour was more adequate, but he remained capricious and was seeking the attention of nursing staff. At that time mild cognitive decline was observed (MMSE=25).

He remained euthymic for five months. Blood counts were regularly checked because of myeloproliferative disease. Total leukocyte count was increased ($12\text{-}17x10^9$/L) with decreased lymphocyte count (13-19%), increased eosinophil count (7-17%), and normal levels of neutrophils. Haemoglobin levels ranged from 126 to 140 g/L, mean erythrocyte volume from 97-103 fl, and thrombocyte counts from $430\text{-}740x10^9$/L. Other laboratory tests were not done.

When mild depression was noticed at the age of 86, escitalopram (5 mg once a day) was prescribed. Clomethiazole 400 mg in a single evening dose was added two days later because of insomnia. The next day the dose of escitalopram was increased to 10 mg daily. Three days after increasing the dose of escitalopram patient reported visual hallucinations of raging fire and bloody meat, he also reported smelling burnt flesh. Sudden change of mental state was described as hallucinatory state, so flufenazine 3 mg daily was prescribed. Hallucinations ceased, but he remained anxious, scared, disoriented and restless during nights, while he was tired and hypobulic during the day.

Six days later the patient was transferred from his ward to intensive care unit where escitalopram, clomethiazole and flufenazine were discontinued. He quickly became more relaxed, his sleep improved and daily activities restored. Hydroxyurea 1000 mg bid, acetylsalicilic acid 100 mg, digoxin 0.1 mg, carvedilol 3 mg, and pantoprazole 20 mg, iron (III)-hydroxide 200 mg daily remained his prescribed drugs.

Residual mild depression was later not treated with any antidepressant, outbursts of verbal aggression were rare, he reported insomnia only occasionally. Three months later he was admitted to nursing home with diazepam 2 mg daily, hydroxyurea, acetylsalicilic acid, digoxin, carvedilol, esomeprazole and folic acid.

DISCUSSION

For effective treatment of delirium establishing the correct diagnosis is necessary, followed by identifying and removing the underlying cause of delirium. In addition, symptomatic and supportive therapy is usually used. Not only are symptoms and signs of delirium frequently overlooked, but they can be overlapping with other drug side effects, such as serotonergic syndrome, which can present a differential diagnostic dilemma (Pisk et al. 2009). One published case in our review could be attributed to serotonergic syndrome (Amir et al. 1997).

Due to the clinical course in five published cases SSRIs do not seem to be the main etiologic factor. In those cases delirium is more likely due to lamotrigine (Chistyakova & Amos 2008), bupropion (Chan et al. 2006), and benztropine (Byerly et al. 1996, Roth et al. 1994), although some effect of SSRIs on etiology cannot be excluded. In two of those cases the same SSRI was successfully started again without a delirium (Byerly et al. 1996, Roth et al. 1994).

In five of the cases of our review SSRIs seem to be the main etiologic factor or at least a probable factor in addition to preexisting diseases, medication, and changes due to old age. In two cases delirium was due to escitalopram (our case) or citalopram (Delić & Pregelj 2012), in two cases due to fluoxetine (Roth et al. 1994, Leinonen et al. 1993) and in one case due to paroxetine (Roth et al. 1994). In addition, in two cases of delirium fluoxetine was a possible additional cause of delirium in combination with protriptyline (Paul & Bhtara 1997) and in combination with perphenazine, benztropine, lithium, and clonazepam (Roth et al. 1994).

To render the etiological role of SSRIs even more mysterious, two cases of delirium due to discontinuation of paroxetine (Hayakawa et al. 2004) and fluoxetine (Blum et al. 2007) were described. Blum et al. (2007) described a case of 53 year old female with chronic fatigue syndrome and multiple sclerosis who was receiving fluoxetine 40 mg, modafinil 200 mg, amantadine 200 mg, oxybutynin 30 mg, interferon beta and levothyroxine 88 mcg. After discontinuation of fluoxetine confusion, auditory and visual hallucinations, grandiose delusions and emotional lability developed. Fluoxetine was reinstated and by the following morning the patient had returned to her baseline mental status and was discharged home. Hashimoto and Furuse (2012) even

suggest that fluvoxamin could be a potential drug for the treatment of delirium in older adults due to sigma-1 receptor agonist activity although they emphasise that a randomized double-blind, placebo-controlled study is necessary to confirm this hypothesis.

Pre-existing changes in pharmacokinetics and pharmacodynamics due to old age, and other physical illnesses which are more common in old age may predispose patients to drug toxicity. A large proportion of published cases (3 of 7, which is 42.9 %) occurred at age 65 and over.

It is well known that delirium is more often a consequence of multiple etiologic factors than a consequence of a single one. Delirium may be attributed to several psychotropic drugs with central activity, especially those that alter cholinergic, dopaminergic, and gama-aminobutyric acid (GABA)-ergic neurotransmitter systems (Bourgeois & Seritan 2006) which include: opioids, antihistamines, anticholinergics, benzodiazepines, barbiturates and other sedatives, anticonvulsants, antiparkinsonian medications, corticosteroids, immunosuppressants, cardiovascular medications, gastrointestinal medications, antibiotics, and muscle relaxants.

In our case, the time of onset and resolution of delirium strongly suggest escitalopram as the main etiologic factor. Insomnia, which appeared two days after escitalopram had been prescribed, was likely a prodromal symptom of delirium which fully developed after increasing the dosage of escitalopram. Treatment with citalopram in high doses five years prior to delirum did not cause side effects, which demonstrates that relying only on experience can be misleading in search of the causative agent of delirium. Frailty increases in old age and delirum is a marker of such frailty.

Although in our case combinations of psychotropic drugs were used for the optimal treatment of bipolar disorder in younger age, in old age the best general health and daily activities were achieved using as few psychotropic drugs as possible because of several side effects that were not observed in younger age.

CONCLUSIONS

SSRIs are probably the most often prescribed antidepressants known for their favourable side-effect profile. Only a few cases of delirium due to SSRIs as the main etiologic factor were published in the last two decades, thus confirming SSRIs are a safe medication to use in old age. However, in an ageing patient even SSRI that was previously successfully used can still cause delirium. Additional care is therefore advised.

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