New insight into the neuropsychiatric side effects of protease inhibitors

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The adverse effects of anti-retroviral drugs should be considered by both medical and psychiatric clinicians for mental health problems in HIV positive patients. This case report describes the development of psychiatric complications in a patient recently commenced on protease inhibitors which then seemingly improved with a switch to an HIV integrase inhibitor.

There is little information on the neuropsychiatric side effects of HIV protease inhibitors (PIs), and these are not listed in drug information literature. We present a case of an HIV-positive man recently commenced on ritonavir and darunavir who experienced psychotic symptoms sufficiently severe to warrant inpatient admission. These symptoms improved considerably once the patient was swapped to raltegravir and he was discharged three days later. There is therefore a strong case to consider PIs as a cause of worsening psychotic symptoms in such patients, and early discussion with HIV physicians to consider a regimen change is warranted.

Case history
Mr D, a 29-year-old HIV positive man, was admitted on 16 January 2014 via the accident and emergency department after presenting with a psychotic event. He described hearing a male voice in the second and third person, commenting on people around him and making derogatory remarks about him. It commanded him to stab his parents with infected needles. He was very distressed by the voice, finding it impossible to cope, and had considered taking his own life because of it. He also reported visual hallucinations, seeing his deceased aunt in the room, snakes on the wall and crows sitting in the window frames. Mr D reported that, since starting ritonavir and darunavir three weeks previously, his symptoms had significantly worsened. Physical examination was unremarkable with no signs or symptoms of localised infection or general inflammatory responses. Mini-Mental State Examination was normal and Glasgow Coma Scale score was 15/15. On mental state examination he appeared paranoid, distracted and anxious with poor eye contact and quiet speech.

He described his mood as very low and objectively appeared depressed. He did not appear to have any formal thought disorder nor delusions, and reported the hallucinations as documented. He was orientated and had good insight into his current issues. Mr D had no contact with mental health services prior to being diagnosed as HIV-positive three years previously. This diagnosis led him to become withdrawn and isolative, and he recognised a clear deterioration in his mood. He took an overdose of 12 paracetamol tablets in September 2012 and was diagnosed with moderate depression that was managed by his GP. He reported occasionally hearing derogatory comments in his head over the past few years, but could not determine whether this was an external stimulus or his own internal thought process. There had been no concern about, nor diagnosis of, psychotic illness previous to this episode.

Diagnosis and treatment
Mr D’s infectious diseases team were contacted on 17 January 2014 for advice on whether his presentation could be related to his recent commencement of ritonavir and darunavir. This was seen as a possibility and so he was therefore swapped to raltegravir. His psychiatric team agreed to commence olanzapine 5mg nocte at the same time. Over the next three days Mr D made a remarkable recovery, reporting a significant improvement in the auditory hallucinations and not reporting any further visual hallucinations. Steady state of olanzapine is not achieved until between seven and 12 days, and so we cannot attribute his improvement to this drug.

He engaged well with staff and peers and went on leave successfully with his family. By 21 January 2014 it was felt by the team, the patient and his family that discharge with input from the Early Intervention Service would be appropriate and so he left the
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ward. At the point of discharge it was planned that the patient should remain on olanzapine with the intention that this be reviewed by the community psychiatric team based on how his mental state fared in the long term.

Discussion
There has been little research into the neuropsychiatric side effects of PIs. In 2005 Hawkins et al. compared neuropsychiatric disturbance reported after four weeks of being commenced on efavirenz or PIs, and found that symptoms were significantly worse in the efavirenz group. They did not, however, feel that the symptoms reported by the PI group were sufficiently significant to warrant further review. Five years later, Winston et al. undertook a randomised prospective study that showed no difference in the rate of new neuropsychiatric adverse events seen in patients commenced on PIs compared to the control group kept on nucleoside analogues. We were unable to find any other case reports documenting psychotic symptoms in patients commenced on PIs.

Interestingly, the HIV integrase inhibitor raltegravir, to which the patient was switched, has a more widely documented profile of psychiatric side effects. Despite this, the switch was made based on the clinician’s opinion of the higher clinical importance of managing the primary HIV infection, using current treatment guidelines on swapping between therapies.

This case has several significant and relevant implications. It has shown a rare side effect of PIs in a patient with a history of depression that should be considered by clinicians from both medical and psychiatric specialties in their future practice.

From a pharmacological perspective, the authors are not aware of any research that compares the relative pharmacokinetics of PIs and integrase inhibitors that could account for their different neuropsychiatric effects in this patient. It also demonstrates the importance of interdisciplinary communication between teams and the need to listen carefully to patient ideas as to the causes of their illness.

By highlighting this case we hope to increase awareness and stimulate further research into this problem.

Future research
• What is the incidence of new-onset psychiatric symptoms in patients commenced on PIs?
• What is the psychopharmacology behind this presentation?
• Should prescribing guidelines be revised and updated in light of this case report?

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References

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