Reviewer's report

Title: Optimising plasma levels of clozapine during metabolic interactions: a review and case report with adjunct rifampicin treatment.

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Reviewer: Virginio Salvi

Reviewer's report:

The case report submitted to the journal is well written and covers a topic of clinical relevance. Indeed, it is important to produce more data on drug-drug interactions in psychiatric patients with serious medical comorbidity. However, this one does not seem to add much to the extant literature, seeming just like a confirmation of a previous case report that showed decrease in clozapine plasma levels due to rifampicin administration (Joos et al., 1998). Therefore some improvements are needed in order to be published:

Major compulsory revisions

1. The authors do not really explain what is the course of psychotic symptoms during rifampicin treatment. Being the patient that severe, it is of outmost relevance to report, with the help of rating scales, the course of psychotic symptoms with regard to suboptimal clozapine levels.

2. The authors state that the patient was taking lamotrigine “as both a mood stabiliser and for seizure prophylaxis.” It should be noted that rifampicin alters lamotrigine pharmacokinetics by induction of the hepatic enzymes responsible for glucuronidation, leading to increased clearance and reduced half-life (Ebert et al., 2000): thus, a possible diminished efficacy of lamotrigine should be taken into account, and should be reported. Furthermore, being the patient diagnosed with schizoaffective disorder, it would be interesting to check whether there have been fluctuations in mood due to a lesser mood-stabilizing efficacy. Again, a mood disorder rating scale (such as, for instance, CGI-BP) should have been administered.

In conclusion, to be worth publishing it, the authors should report more thoroughly on the course of psychiatric symptoms during TB treatment. They should report rating scales scores at some key time points and discuss their variations with that of clozapine plasma levels.

Minor essential revisions

In the background section (page 2, line 13) it is said that “fluoxetine and fluvoxamine, and smoking cigarettes, through the effect of aromatic hydrocarbons, is recognised to inhibit CYP1A2 or the other relative isoforms, while treatment with antibiotics such as erythromycin, and intake of caffeine induces CYP1A2 SSRIs and tobacco smoke inhibit CYP1A2, while some
antibiotics and caffeine induce it.” The sentence is wrong: some SSRIs, caffeine, and some antibiotics inhibit the cytochrome, while smoking induces it. Please correct.

Discretionary revisions
The Authors note that, after moxifloxacin and pyrazinamide were stopped, clozapine plasma levels showed a stable rise for three weeks: they conclude that “the cause for this remains uncertain”. Moxifloxacin, a 4th-generation quinolone antibiotic, is mainly excreted by glucuronide conjugation. As previously said, rifampicin induces this II-phase metabolism pathway, thus decreasing moxifloxacin plasma concentrations, although on the other hand moxifloxacin does not seem to alter rifampicin pharmacokinetics (see Ramachandran et al., 2012). Pyrazinamide also does not seem to alter other drugs pharmacokinetics (see Nishimura et al., 2004). Although it might be true that the extant knowledge on moxifloxacin/pyrazinamide pharmacokinetics does not allow explaining the observed phenomena, Authors might discuss this point more thoroughly.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.