Author's response to reviews

Title: Successful treatment of schizophrenia with melperone-augmented haloperidole in a patient with phenotypic evidence for CYP2D6 ultrarapid metabolizer status: a case report

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Author's response to reviews: see over
Dear Editor,

thank you for your friendly electronic mail from October 2nd 2011 and the favourable overall assessment of our manuscript made by the referee. We also appreciate his valuable suggestions for further improving the paper.

We have carefully considered all suggestions made by the reviewer and have revised the manuscript accordingly. All changes in the manuscript are highlighted with bold letters.

In the following, we will respond to the referee’s comments on an item-by-item basis.

Referee #1 (Salih Selek):

We thank the referee for his second assessment and the suggestions made for further improving the paper:

1. The referee suggests to specify the changes that were done based on his recommendations from his first review. In order to clarify our modifications we give a more detailed illustration of our changes in the following. The order of the following points corresponds to the order of the points of the first review of referee#1 (Salih Selek). They are basically formed by our original respond to the first review and now provide, as advised, more details for particular passages in order to enable the reviewer to track our initial modifications. The changes that were made within the first revision are still highlighted with bold letters in the manuscript.

   • (point 1 of first review): The title has been changed accordingly to “Successful treatment of schizophrenia with melperone-augmented haloperidole in a patient with phenotypic evidence for CYP2D6 ultrarapid metabolizer status: a case report” by Gahr, Gastl, Kölle, Schönfeldt-Lecuona and Freudenmann.
evidence for CYP2D6 ultrarapid metabolizer status and non-response to amisulpride: a case report”. According to the second review of referee#1 was changed again (as elucidated in point 4 of the current response letter) to “Successful treatment of schizophrenia with melperone-augmented haloperidole in a patient with phenotypic evidence for CYP2D6 ultrarapid metabolizer status: a case report”. In addition, the term “schizophrenic” was changed throughout the manuscript to “patient with schizophrenia” as suggested by the referee.

• (point 2 of first review): We agree with the referee’s statement of existing literature that provides treatment recommendations. But, in contrast, evidence based guidelines for patients with schizophrenia, CYP2D6 UM status and non-response to amisulpride are lacking. With our report we primarily want to contribute to the set of available experience with this particular treatment situation. Creating true evidence based guidelines requires a sufficient pool of data, to which we contribute with our report. In order to avoid the misunderstanding that is stated by the referee we changed the term “treatment recommendations” to “evidence based guidelines” in the abstract, introduction and discussion section. The original term “(…) any treatment recommendations for this patient population” in the introduction section of the abstract was replaced by “(…) evidence based guidelines for this particular constellation.”

• (point 3 of first review): The core message of our report was limited in order to avoid generalisation, as suggested by the referee, in the abstract and conclusion section. The conclusion section of the abstract was completely rewritten and the former paragraph “This report yields the melperone-augmented haloperidole as a feasible pharmacological strategy in the described situation and gives evidence for the potential of melperone to inhibit CY2D6” was replaced by “This report yields melperone-augmented haloperidole as a possible pharmacological strategy in the described situation. In addition, our observations support the available evidence for the potential of melperone to act as an inhibitor of CYP2D6.” Also the conclusion was completely rewritten and the former paragraph “We hypothesize that this combination can be a useful strategy in schizophrenic patients with CY2D6 UM status and previous non-response to amisulpride” was changed to “We hypothesize that melperone-augmented haloperidole can be considered as a possible treatment strategy in patients with schizophrenia, CYP2D6 UM status and previous non-response to amisulpride”. The second sentence of the conclusion section “Furthermore, this report shows that melperone is a possible inhibitor of CYP2D6” was replaced by “Furthermore, our observation of sufficient haloperidole plasma levels under augmentation with melperone is in line with studies that described melperone as an inhibitor of CYP2D6 dependent metabolism of risperidone [5] and venlafaxine [6].”

• (point 4 of first review): The key word was changed accordingly from “pharmacokinetics” to “pharmakogenetics”.

• (point 5 of first review): The introduction section was rewritten accordingly. Augmentation is now explained more clearly and the paragraph that deals with fluvoxamine-augmentation of clozapine [“In this context, e.g. administering fluvoxamine, a potent inhibitor of CYP1A2 and CYP2D6, together with clozapine, that is nearly completely metabolized in the liver by CYP1A2, CYP3A4 and to a lower extent CYP2D6, is occasionally feasible in the treatment of patients with schizophrenia to facilitate a decrease of the clozapine dose”] was deleted completely due to its insignificant contribution. The term “One possible strategy is to induce pharmacokinetic interactions by means of the added drug with enzymes associated to the cytochrome P450 system (CYP)” was modified to “One possible augmentation strategy is via pharmacokinetic interactions. Here the added agent interacts with enzymes of the cytochrome P450 system (CYP) that is important for the hepatic metabolization of numerous drugs”. In addition, the term “(…) a specific inhibitor of metabolic pathways of the drug to be enhanced, so that decreased doses are necessary to cause sufficient plasma level concentrations” was modified to “(…) a specific inhibitor or inductor of metabolic pathways of the drug to be enhanced, so as to, for example, decreased doses are necessary to cause sufficient plasma level concentrations”. The term
“Within the CYP family (...)” was simply added in front of the particular sentence. Finally, the term “(...) are limited and there are no treatment recommendations in the literature for that situation” was changed to “(...) are limited and evidence based guidelines regarding this particular treatment situation are lacking”.

- **(point 5 of first review):** Quality of English has been improved again with the help of a native speaker.
- **(point 6 of first review):** We already handled this point under our the second sub-point of the first point of this response letter. We changed the term ”treatment recommendations” to “evidence based guidelines” in the abstract, introduction and discussion section. The original term “(...) any treatment recommendations for this patient population” in the introduction section of the abstract was replaced by “(...) evidence based guidelines for this particular constellation.”
- **(point 7 of first review):** We thank the referee for his advice. The manuscript has now been corrected by a native speaker. Typos and grammatical errors are now eliminated.
- **(point 8 of first review):** We now added more clinical information an explained the course of diagnosing schizophrenia at this patient. For that purpose we added the paragraph “Due to numerous treatments in our clinic during the last 10 years the patient was well known and the diagnose of schizophrenia has been secured based on several psychotic episodes and unremarkable somatic examination including analysis of cerebrospinal fluid, electroencephalogram and MRI scan of the brain” in the case description section.
- **(point 9 of first review):** Quetiapine was tapered of due to its missing antipsychotic effect in this patient after one week of reliable oral intake of 700mg/day. Increase of its dosage was not performed against the background of sufficient quetiapine serum levels. This circumstance is now stated more clearly in the case presentation section by adding the term “In view of sufficient quetiapine serum levels (854 ng/mL; quetiapine 700 mg per day) a treatment trial with an increased dosage of quetiapine was not performed”. This term was modified again subsequent to the second review (see point 3 of the current response letter).
- **(point 10 of first review):** We mentioned the metformine treatment in order give a complete overview of the patient’s medication. The indication of metformine is now explained in detail (metabolic syndrome) by adding the term “[...] due to adiposity and metabolic syndrome (body weight 102,8 kg, body height 156 cm, BMI 42,2 kg/m²)” in the case description section.
- **(point 11 of first review):** this point is now handled under point 4 of the current response letter (see below).
- **(point 12 of first review):** Unfortunately we did not use rating scales. Evaluations were made based on the clinical impression of three psychiatrists that were involved in the patient’s treatment over the whole period of time. The criterion was the reduction of psychotic symptoms (auditory hallucinations) and disorganized speech and behaviour. These aspects remained unchanged during amisulprid treatment.
- **(point 13 of first review):** Haloperidole decanoate was administered in a dose of 150 mg, risperidone was given orally up to 8 mg per day. The missing doses are now presented by modifying the former term”(...) recent ineffective treatment attempts with usual doses of risperidone and haloperidole-decanoate” to “(...) recent ineffective treatment attempts with risperidone (up to 8 mg per day) and haloperidole-decanoate (up to 150 mg per injection)”.
- **(point 14 of first review):** The procedure of phenotypical testing for CYP2D6 metabolizer status is now explained in detail in the case presentation section by adding the paragraph “This phenotypical testing was performed by taking a blood sample (120 mL) exactly 1 hour after the oral application of 40 ml NeoTussan® cough syrup (111 mg dextromethorphan/ 100 g suspension). Blood was analysed for metabolites of DM and MM, that are substrates of CYP2D6. The DM/DO and MM/HM ratios are surrogate parameters for the CYP2D6 activity”.
- **(point 15 of first review):** As stated in the text, trazodone was administered for augmentation of haloperidole. Trazodone is a common CYP2D6 inhibitor and thus a
possible agent for augmentation of haloperidole (in order to increase haloperidole serum levels with unchanged haloperidole dosage). Since the treatment with amisulpride (that is eliminated on a renal pathway) failed we did not try other antipsychotics.

- (point 16 of first review): We wanted to call attention to the circumstance that in our case haloperidole plasma levels increased after escalation of haloperidole dosage and simultaneous add-on therapy with melperone. Thus, it is not clear to what content melperone really contributed to the elevation of haloperidole serum levels. To prove an essential involvement of melperone (relevant CYP2D6 inhibition) discontinuation of melperone and repeated measurements of haloperidole serum levels (without melperone) should have been performed. Since the intractable clinical situation was stable under treatment with haloperidole and melperone for the first time we refrained from discontinuation of melperone in order to avoid relapse. In order to clarify this we reformulated the respective paragraph. The paragraph “(…) it is possible that sufficient haloperidole plasma levels were induced simply by elevated haloperidole doses with regard to comparatively low doses of melperone. Discontinuation of melperone and repeated measurements of haloperidole serum levels could have provided clarity. However, due to the unstable clinical situation this attempt was not performed” was modified to “(…) it is conceivable that in our case sufficient haloperidole plasma levels were simply a consequence of escalated oral haloperidole doses and to a lesser extent induced by melperone-mediated CYP2D6 inhibition. Discontinuation of melperone and repeated measurements of haloperidole serum levels under the removed influence of melperone could have provided clarity. However, due to the unstable clinical situation and first-time treatment success with melperone-augmented haloperidole we refrained from any modification of the psychopharmacotherapy.”

- (point 17 of first review): We already cited two studies in the discussion section (reference number 5 and 6). In the conclusion we now make a connection between these studies and our clinical observations by adding the paragraph “Furthermore, our observation of sufficient haloperidole plasma levels under augmentation with melperone is in line with studies that described melperone as an inhibitor of CYP2D6 dependent metabolization of risperidone [5] and venlafaxine [6]”. This change has already been explained under subpoint 3 of point 1 of the current response letter (see above).

2. As suggested by the referee the term “(…) the causation of (…)” was replaced by “(…) via (…)” in the beginning of the introduction section.

3. We fully agree with the referee’s opinion concerning the short treatment attempt of quetiapine. One week treatment with quetiapine 700mg/day is definitively too short to judge the attempt as failed. In our case quetiapine was discontinued due to sufficient plasma levels and the remarkable obesity of the patient. Avoiding a possible induction of further weight gain by quetiapine was an additional reason to quit quetiapine. This in now stated in the text by adding the term “(…) and remarkable obesity (…)” in the case description section.

4. Regarding available treatment guidelines for schizophrenia we completely agree with the referee’s that it is incorrect to judge unresponsiveness after three weeks of amisulpride treatment. We apologize for our inaccurateness. But, according to the treatment guidelines of the German Association for Psychiatry, Psychotherapy, and Neuroscience (DGPPN, see at: http://www.dgppn.de/fileadmin/user_upload/_medien/download/pdf/kurzversion-leitlinien/s3-praxisleitlinien-bd1-schizophrenie.pdf) it is appropriate to switch the antipsychotic in case of clinically insufficient antipsychotic effect at the earliest after 2-4 weeks, as done in our case. But, however, it is wrong to state that the patient was a non-responder to amisulpride. We therefore changed all phrases in the manuscript that described “unresponsiveness” in order to avoid this misunderstanding. The title was changed to “Successful treatment of schizophrenia with melperone-augmented haloperidole in a patient with phenotypic evidence for CYP2D6 ultrarapid metabolizer status: a case report” by eliminating the term “and non-response to amisulpride”. In the case presentation section of the abstract we replaced the term “(…) previous non-response to (…)” to “(…) insufficient antipsychotic effect of (…)”. In the Conclusion section of the main document we changed the term “(…) previous non-response to
“(...)” to “(...) insufficient antipsychotic effect of (...”). In the case description section we did not use the term “non-responder” to explain our treatment modification.

5. The manuscript was again corrected by a native speaker and further improvements were made.

We again thank the referees for the helpful comments, hope that the changes now qualify the manuscript for publication in the *Journal of Medical Case Reports*, and look forward to hearing from you.

Yours sincerely,

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