Reviewer A

Comment 1: Overall, this is a fair review on WD. Since the title is “Therapeutic strategies in Wilson disease: how do they operate?”. The long but incomplete discussion of pathophysiology, clinical presentation and diagnosis is not needed at all, and should be summarized in a few sentences in the introduction.

Reply 1: We purposely chose the inclusion of pathophysiology to lead the reader to the proposed mode of action. To make that clear we changed the title of the article accordingly (page 1, lines 4-7).

Comment 2: Page 5. Only in about 50% of the patients the disease manifests. I think this is wrong, what is the evidence for this statement?

Reply 2: We removed the sentence.

Comment 3: Page 6, line 128 Signs of cirrhosis are rather late indicators. This is not true (see ref.16)

Reply 3: The sentence is rephrased.

Comment 4: Page 6, lines 132-133. Recently, an association with antinuclear antibodies (ANA) elevation was suggested to be responsible for transaminase elevation (22). This is neither new nor important. Ref 22 is just submitted. There are numerous case reports in the literature, that some patients cause a diagnostic dilemma. However, >95% of patients with Wilsonian hepatitis have no detectable autoantibodies. So this statement is nonsense.

Reply 4: Sentence and reference are deleted.

Comment 5: Lines 240-2 Challenging is the observation that with liver transplantation the disease is cured and does not require further copper controlling therapy. This is incorrect, what is the evidence for this statement?

Reply 5: Sentence is rephrased and a reference is added.

Comment 6: Line 257-8 The liver copper content increases with time. This is incorrect (see Ferenci et al. Clin Gastroenterol Hepatol. 2005)

Reply 6: The statement has been changed and a new reference was added.

Comment 7: Lines 271-3 chelator therapy the enhanced copper excretion lasts only
Wrong: it depends how you measure urinary copper excretion (on drug or after drug holiday). I treat WD pts. for more than 30 years, not a single one had a normal copper excretion on D-Pen.

Reply 7: The sentences are now corrected (starting page 13, lines 313).

Reviewer B
Comment 1: The authors submitted a review entitled “Therapeutic strategies in Wilson disease: how do they operate?”. The manuscript is a little broader, also describing the basic pathophysiology of the disease. However a little more than 50% deals with the treatment and with some therapeutic/strategic considerations. Their calculation that the therapy will only remove a small fraction of whole body copper is quite original and interesting. They evidently have deep knowledge of the disease and the literature, which is important for such a review to have impact.
Reply 1: We appreciate to rear that in addition to treatment a considerable portion of the review deals with pathophysiology. This, however, was important to comprehend the mode of therapeutic action. Accordingly, we changed the title. We like the positive attitude towards our calculation of potential liver copper removal by chelators.

Comment 2: It is easy to read and well structured. That said, the language contains many expressions that are not native English and to an extend that will disturb many potential readers. I suggest the paper is revised by a person with better control over the English language.
Reply 2: We took the suggestion for revision of the English by a person with better control over the English language.

Comment 3: Maybe it should be mentioned that none of available therapies have been examined in RCTs.
Reply 3: We included a statement about missing RCT for the available therapies (page 9, line 202 and page 17, line 413.

Comment 4: Line 5. Is WD really “well treatable ?” After all, a number of patients will have residual disease after years of treatment, both hepatologic and neurologic (as even stated at the end of the abstract).
Reply 4: We deleted the term “well treatable”.

Comment 5: Lines 13-15. “..the option of a direct measurement of free copper is
preferable over the present less reliable calculation of this fraction. “I do not disagree but actually that problem is not discussed in the manuscript. So either remove it from the abstract or deliver the arguments in the paper.

Reply 5: We discussed now calculated and measured free copper concentration (page 8, line 176 and page 17, lines 408 ff.).

Comment 6: Line 36. It is not clear what is meant with “incorporated into the systemic iron delivery system transferrin”
Reply 6: We rephrased the sentence “incorporated into transferrin for iron delivery to the system utilizing transferrin receptors (page 3, lines 60-62).

Comment 7: Line 46 Don’t understand the hyphen
Reply 7: The hyphen is removed in the revised version.

Comment 8: Line 57 Make sure Reference 7 is correct in this position.
Reply 8: Reference-# 7 has been taken out at that position.

Comment 9: Line 62. I do not understand the last three words “also containing Cu1+”. Could they be omitted?
Reply 9: We rephrased the sentence (page 4, line 88).

Comment 10: Line 70. “requires” must be a wrong word.
Reply 10: We exchanged “requires” by another phrase (page 5, line 95).

Comment 11: Line 79. Please add a reference the sentence that ends “... they are in close proximity”.
Response 11: We could not find a reference. Therefore, we rephrased the respective sentence.

Comment 12: Line 80. Add a reference for the sentence “Another explanation ..neurons”.
Reply 12: For the issue of ATP7B in neurons a new reference is added.

Comment 13: Line 82. Not only Iron but also Cu accumulates in the basal ganglia
Reply 13: The cause of neurological manifestation could be due to neuronal ATP7B associated structural damage, iron or copper overload. This is now discussed (page 5, lines 104-106).
Comment 14: Line 83. The sentence reads as if the KF ring is caused by iron, and I thought it was Cu. Please be sure you are correct.
Reply 14: The KF-ring is due to copper accumulation. This is now clearly stated (page 5, lines 114-115).

Comment 15: Line 97. “Only in about 50% of the patients the disease manifests”. If you mean that the penetrance is only 50% that in conflict with common wisdom. Please explain. Provide a reference.
Reply 15: We removed the sentence because it was just a guess.

Comment 16: Lines 104-106. There are other hypothesis, i.e. variants in the ATOX1-gene etc. Maybe worth mentioning (could have impact on treatment).
Reply 16: We added a sentence referring to the ATOX1 and aceruloplasminemia.

Comment 17: Line 111. Make sure the formula is correct. In the EASL guideline the factor is 3.15 (page 7, line 188).
Reply 17: We changed the factor according to the actual guidelines to 3.15 (page 7, line 146).

Comment 18: Line 114. The Rhodamin stain method is not the gold standard. Only the liver copper determination is the Gold Standard. It is rather controversial how well the Rhodamin method works. If you want to defend it, provide references.
Reply 18: We rephrased the sentence and mentioned Rhodamin stain for detection of lysosomal copper.

Comment 19: Line 138-140. I don’t understand how “a normal urinary copper excretion” is the “most reliable pathophysiologic parameter for disease manifestation”. Please amend and provide references for the opinion.
Reply 19: This was a wrong statement which we have deleted.

Comment 20: Line 142. Provide reference for the last sentence.
Reply 20: We provided a reference as well as our own experience (page 8, line 176 ff).

Comment 21: Line 145. Provide reference for the <1 year life expectancy
Reply 21: Life expectancy is 40 years. We also added a reference. (page 8, line 183)

Comment 22: Line 156. “Considerable” is a wrong word.
Reply 22: We changed the sentence.

Comment 23: Line 167. The dosage of B6 is high compared to international guidelines, please add a reference.
Reply 23: We suggested now a dose of 25-50 mg vitamin B6 daily (page 9, line 208).

Comment 24: Line 172. “.. chelator (Table1)”. Add a reference.
Reply 24: We added a reference (page 9, line 212).

Comment 25: Line 177. Most of my patients need a higher maintenance dose than 600 mg/d. Add a reference.
Reply 25: We provided the range of 600-900 mg and a reference (page 9, line 217).

Comment 26: Line 187. Ad reference to the sentence about ANA often seen after initiation of penicillamine.
Reply 26: Reference is added (page 10, line 227).

Comment 27: Lines 190 and 194. Is trientine less effective (line 190) or “as effective” (line 194) as penicillamine?
Reply 27: We changed to “as effective as D-penicillamine” (page 10, line 233 ff).

Comment 28: Line 198. Add a reference to the sentence “It is claimed ... event profile”. I don’t think there is evidence behind this claim. Provide the evidence or delete the sentence.
Reply 28: We deleted this sentence.

Comment 29: Line 223. Add a reference for this sentence.
Reply 29: We added a reference.

Comment 30: Line 257-258. Please provide a reference for the statement that “liver copper content increases with time”. I think that is more variable.
Have a look at
Line 272. I do not think 24 U Cu returns to undetectable levels in WD patients after 1
year of treatment.
Reply 30: We changed the paragraph, reversed our statement and included references (page 12, lines 296-299; Ref 59 & 60).

Reply 31: We are not sure where you indicated to put additional references because our line counting was slightly different. However, we added more references.

Comment 32: Line 306. Make sure the references really provide evidence for the statement.
Reply 32: We checked again all the references and confirm that they provide evidence for the statement.