Reviewer's report

Title: Evaluation of patients on sertindole treatment after failure of other antipsychotics: a retrospective analysis

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Reviewer: Nicholas Moore

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General
Evaluation of patients on sertindole treatment after failure of other antipsychotics: a retrospective analysis
by JM Azorin et al

This paper describes the attempt to demonstrate that there exist some patients that are responsive to sertindole when other antipsychotics have failed, either because of poor tolerability or poor efficacy. This study was done in the context of sertindole’s suspension from the market for a suspicion of increased mortality from cardiovascular events. To properly assess the risk-benefit ratio of sertindole, it was necessary to demonstrate some benefit of sertindole over other antipsychotics, in some patients. Since at the time the drug was suspended it was not possible to do a randomized controlled trial. So that the authors identified patients who had been treated with sertindole after failure of another neuroleptic.

a) These patients were identified in another study, the sertindole surveillance study – is this ESES? {Peuskens, 2007 #385}.

All these patients were taken off sertindole when the drug was suspended, and then eventually put back on sertindole, under a named-patient compassionate use program, for which prescribers had to ask for the drug specifically.

These patients were identified, and their disease history rebuilt retrospectively, to understand what had happened and why, and document patient status during each of these four phases.

This study therefore demonstrates that there is a group of patients (frequency unknown) who seem to respond to sertindole better than to other neuroleptics, and this occurred twice. In this aspect, this is in fact a case series with positive rechallenge, demonstrating the reality of the effect. Were this a series of adverse reactions, there would be no doubt of its reality.

This is the main result of the study. The methodology is as good as it could be under the circumstances, and the paper faithfully describes the process with some caveats.
There are however some points to be amended:

b) it should be stated that this is an observationnal study (including in the abstract)

c) it is not quite clear whether the clinical data on patient status during the different periods was reconstructed retrospectively from the psychiatrists' recollection of it, or whether it was abstracted from the case notes by a committee blinded to the period (1, 2, 3, 4) and the treatment. I suspect it was the former, in which case these results, though interesting, have little value and could be omitted at least from the abstract, and given mainly as supportive.

d) the real value is in the data that was prospectively recorded and could not be influenced by post-hoc appreciation, i.e. the hospitalisation and possibly the marital or societal status, especially if the latter was recorded in the case notes at the time. The paper should really be focused on these objective data, if the subjective were not reassessed blindly.

e) in study design (p6) it is stated on line 6 that after an initial treatment period of at least 6 months, all patients were switched to sertindole: this gives the impression that it was a voluntary act designed in the study, whereas this was an observed event, related to poor tolerability of efficacy of the initial drug(s). this should be stated somewhere in the study design paragraph. Maybe something like had been switched rather than were switched, to emphasize the passive rather than active nature of the switch (from the study point of view).

f) in data analysis, the main outcome should be the objective outcome of hospitalisation, suicide attempts, employment status and stable relationship, with support from the retrospectively defined subjective assessment by the psychiatrist.

h) table 3 could be changed to a figure of patient disposition, showing that
   - 344 patients had been selected as having had at least 6 months of initial non-sertindole treatment for schizophrenia, which was changed to sertindole because of treatment failure, and had not had treatment failure during at least 6 months of sertindole treatment.
   - of these, 211 were switched to another neuroleptic after sertindole suspension (what happened to the 131 others: was the antipsychotic treatment stopped? was there a time constraint on 3rd period treatment (at least 6 months)?
   - of these 211, 57 were switched back to sertindole because of poor efficacy or tolerability of non-sertindole treatment. We presume the 156 who were not switched back to sertindole responded reasonably well to the other neuroleptics, or the psychiatrist did not want to go through the hassle of filling all the forms needed to obtain sertindole for their patients?

Of course, these 57 patients are the ones who most needed sertindole. The number is irrelevant because the method does not allow for precise frequency computation. Should these be considered as % of initial population (1432
patients), or % of the patients included in the study (344), i.e. around 17%, or of
the patients put on other neuroleptics after sertindole was suspended, i.e. 211
(25%).

Major Compulsory Revisions (that the author must respond to before a decision
on publication can be reached)
None really. Possibly improve the abstract, emphasizing more the objective than
the subjective findings

Minor Essential Revisions (such as missing labels on figures, or the wrong use of
a term, which the author can be trusted to correct)
see above

Discretionary Revisions (which the author can choose to ignore)
Please read comments above. It would be nice to improve the abstract.

What next?: Accept after minor essential revisions

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 have worked as a consultant with Lundbeck concerning the suspension of
sertindole, and am the chairman of an independent safety committee overseeing
a clinical trial of sertindole.
I have no other competing interests.