**Manuscript:** the potential role of atypical antipsychotics in the treatment of panic disorder

**Outcome:** accepted pending major revisions

**Comment:** The authors reviewed the literature on the effects of anti-psychotics in the treatment of panic disorder (PD). PD is traditionally treated with psychotherapy, SSRIs and anxiolytics. Given the low success rate of SSRIs in PD, it is certainly necessary to explore and review the literature on alternative pharmacological treatments for PD. This manuscript has therefore potential to make a significant contribution to this research field and the clinical practice. However a stronger rational and additional critical appraisal and discussion of the implications and meaning of the current findings is necessary to make a determination about the use of anti-psychotics in the treatment of PD. The authors should revise and restructure their manuscript to address the comments here below. Thorough proofreading and editing of the manuscript before resubmission is recommended.

**Abstract:** Addition of a couple of sentences on background and specific aims of this review would be helpful. Results section should be re-written and relevant findings highlighted. In the conclusions the authors should focus on the meaning and implications of the findings.

**Background:** the rationale of the paper should be improved in both the abstract and the background section of the manuscript. The authors should address the fact that certain symptoms of panic disorder are not specific to anxiety disorders and present in other disorders such as psychotic disorders. Given the increasing body of literature on the shift from a categorical to a dimensional understanding of mental illness (e.g. DSM-5 vs RDoC), more information on the effects of SSRIs and antipsychotic medications on cognitive performance and neural activity is necessary. More background information should be provided in terms of mechanisms of action of antipsychotic treatments and SSRIs, these mechanisms of action possibly differ between panic disorder and anxiety disorder and how panic disorder differ from and other anxiety disorders (GAD, PTSD). Panic disorders traditionally respond better to psychotherapy compared to medications. This should be briefly discussed as well. Please discuss side effects that may appear over time following anti-psychotic treatments vs SSRIs. In the manuscript the authors mention that the aim of the study is s to measure efficacy and tolerability of these treatments, but the abstract only mentions efficacy. It is also important that the authors explain how they define efficacy and tolerability and based on which criteria do they plan to assess these. The authors could also list names of traditional anti-psychotics in this section to facilitate the understanding of the findings.

**Methods:** Please add a flowchart (for example a PRISMA or CONSORT graph) to describe the process of inclusion/exclusion of studies and number of papers reviewed. Also the description of what kind of study designs were included, types of outcomes (clinical scales? Cognitive measures?), methodological quality (how did the authors evaluate the reliability of the findings? Did you conduct a quality assessment?). How many people reviewed these papers? Did the authors filter papers by age/gender or other demographic characteristics of the sample? Did they try to include unpublished findings to reduce the publication bias?

**Results:** the authors mention somewhere the average daily medication dose for for the medications tested in these studies to help a non-clinical audience understand if doses were higher/lower than the average. The authors should explain statistical terms in “lay words”. For example Page 6, line 33 what does a treatment by time interaction means in terms of the study findings. Duration and severity of illness as possible confounders should be discussed. Further it is unclear why on page 6 line 36 the authors discuss findings of the 113 participants in Sheehan et al.’s study when they previously mentioned that only 108 participants completed the study. Overall a more critical appraisal of the findings and what they may mean is required. For example the authors could have compared quetiapine XR to risperidone in terms of composition, biological targets, estimated timing of medication effects. Same could be done for the other medications mentioned in this section. Page 7, line 31: what was the exact p value for this finding? A traditionally accepted statistical threshold is p < .05, hence p<.07 is not necessarily significant. Differences in compliance between the risperidone and paroxetine groups should be addressed. Another interesting issue would be the interaction with other medications that the patients are on. Page 13 Line 53/54: what do the authors think about the development of future placebo, double-blind trials, could this be a better option? Did previous studies explore whether age/gender/IQ and socio-economic status affect the effects of medication on remission? And did they check how long these effects last for? Did they differ from those observed in patients taking SSRIs? Was risk of relapse ever discussed in the studies that the authors reviewed? And how was compliance measured in these studies? These are important factors to address.

**Discussion:** I would revise it by addressing the comments I made for the results section, e.g. pharmacokinetics, study design, compliance, diagnostic criteria/comorbidity etc. Do the authors see antipsychotic as a possible adjuvant treatment or rather as replacement for SSRIs, and what are their thoughts regarding anxiolytics versus anti-psychotic medication. The authors could add a few sentences on whether the effects of antipsychotics on panic symptoms as a comorbid condition may differ from those in panic disorder.

**Tables:** I would recommend to add columns on daily medication doses, N of subjects per treatment group, scales/outcome measures, duration of illness, effect size of results, and outcome (e.g. positive (+) or negative (-).