


2018

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## Recommended Citation

ORAL HY. Lurasidone is not associated with risk of QTc prolongation. Clin. Res. Prac. 2018 Sep 14;4(2):eP1679. doi: 10.22237/crp/1536278400

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# Lurasidone is not associated with risk of QTc prolongation

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**ABSTRACT** A critical appraisal and clinical application of Meltzer HY, Cucchiaro J, Silva R, Ogasa M, Phillips D, Xu J, Kalali AH, Scheizer E, Pikalov A, Loebel A. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo- and olanzapine-controlled study. *Am J Psychiatry*. 2011 Sep;168(9):957-67. doi: <https://doi.org/10.1176/appi.ajp.2011.10060907>.

**Keywords:** *lurasidone, QTc prolongation, antipsychotic, antipsychotics, schizophrenia*

## Clinical Context

A 60-year-old African American woman with schizophrenia and obesity presented to the emergency department with her daughter, with a complaint of worsened mental status. Due to her QTc interval of 486ms, the team hesitated to increase her home dose of haloperidol. The psychiatry resident suggested lurasidone, a newer atypical antipsychotic, instead.

## Clinical Question

Is lurasidone associated with QTc prolongation?

## Research Article

Meltzer HY, Cucchiaro J, Silva R, Ogasa M, Phillips D, Xu J, Kalali AH, Scheizer E, Pikalov A, Loebel A. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo- and olanzapine-controlled study. *Am J Psychiatry*. 2011 Sep;168(9):957-67. doi: <https://doi.org/10.1176/appi.ajp.2011.10060907>

## Related Literature

These articles were found on PubMed, by searching “antipsychotics,” “lurasidone,” “QTc” or “QT” and “safety” in different combinations, filtered by clinical trials. Searching “lurasidone” and “QTc” yielded one trial, while searching “lurasidone” and “QT” yielded none. Searching “lurasidone” and “safety” yielded 17 trials. Those that did not specifically discuss QT interval, or did not address schizophrenia in US adults, were excluded from discussion. The similar articles sidebar was also used to find similar trials.

According to a 2014 meta-analysis of QTc prolongation with antipsychotics, typical antipsychotics have the highest risk of prolonging QTc, but atypicals like quetiapine, risperidone, olanzapine, iloperidone, and especially ziprasidone have significant risk as well. Atypicals with lower risk include olanzapine, risperidone, and quetiapine. Antipsychotics that have not been shown to prolong QTc are lurasidone, clozapine, and aripiprazole.<sup>2</sup>

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ISSN: 2379-4550

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A 2011 systematic review by Citrome et al. found that lurasidone 80 mg/day was efficacious versus placebo, and was associated with minimal weight gain, no alterations in glucose or lipids, and no prolongation of the QT interval. The strongest evidence given in this review was a meta-analysis of five retrospective studies of patients with an acute exacerbation of schizophrenia. 1004 subjects were treated with lurasidone, 72 with haloperidol, 122 with olanzapine, and 455 with placebo. Mean QTcF (QT interval corrected for heart rate with the Fridericia correction formula) change was minimal for lurasidone. This study was not selected for appraisal because it was not a randomized controlled trial.<sup>3</sup>

The product packaging itself was also cited by this review. The packaging describes a randomized, double-blind trial of 43 patients with schizophrenia or schizoaffective disorder who were treated with doses of 120 mg or 600 mg daily. The maximum increase in QTc interval was 7.5 ms for the 120 mg group and 4.6 ms with the 600 mg group, which the authors interpreted as demonstrating no apparent exposure-response relationship. This study was not selected for appraisal due to the small sample size, lack of placebo control, and incomplete description of the study in the product packaging.<sup>3</sup>

A 2011 study by Potkin et al. looked at adult outpatients with schizophrenia and schizoaffective disorder who were randomized to 21 days of treatment with either lurasidone or ziprasidone. While no significant changes in QTc occurred with lurasidone treatment, the authors themselves state the study was limited due to the short time span of the trial and lack of placebo control.<sup>5</sup> Furthermore, ziprasidone is known to significantly prolong QTc2 so it does not serve as the best comparison.

A 2013 study by Loebel et al. looked at subjects with recent hospitalization for acute exacerbation of schizophrenia. This was a multiregional study with a total of 486 subjects, 151 of which were from the United States. Subjects were randomized to 6 weeks of lurasidone 80 mg, lurasidone 160 mg, 600 mg quetiapine XR, or placebo. There was no significant difference in QTc prolongation between the lurasidone groups and the placebo group. This study was considered for analysis due its large sample size and comparison of lurasidone to both placebo and quetiapine.<sup>4</sup>

A 2011 study by Meltzer et al. looked at inpatients with an acute exacerbation of schizophrenia. This was also a multi-center study, with a total of 478 patients, 286 of which were from the United States. Patients were randomized to 6 weeks of treatment with 40 mg lurasidone, 120 mg lurasidone, 15 mg olanzapine, or placebo. No significant changes were observed in QTcF interval in any of the groups.<sup>1</sup> This study's strengths were its large sample size and comparison of lurasidone to both placebo and olanzapine. Ultimately it was chosen for analysis over the 2013 study because its sample was more representative of a United States population.

## Critical Appraisal

The 2011 study by Meltzer was a Phase III double-blind multicenter randomized controlled trial whose primary goal was to evaluate the efficacy of lurasidone compared to olanzapine and placebo; secondary objectives were evaluating the safety and tolerability of lurasidone compared to controls.<sup>1</sup>

Randomization was carried out via interactive voice response system in a 1:1:1:1 ratio for each of the treatment arms. Baseline characteristics, including symptom severity, age, sex, and race, were similar between all four groups.<sup>1</sup> The results are thus likely unaffected by selection bias.

The interventions given were 40 or 120 mg of lurasidone, 15 mg of olanzapine, or placebo. Blinding was maintained using over-encapsulation of medications<sup>1</sup>, so there is low risk of observer-expectancy effect.

Rates of discontinuation were 6.7% in the lurasidone 40 mg group, 11.8% in the lurasidone 120 mg group, 6.5% in the olanzapine group, and 8.6% in the placebo group, therefore attrition was relatively similar between groups. Intention to treat was used for the primary efficacy analysis of the study.<sup>1</sup>

Lurasidone was found to be efficacious, with a significant decrease found by ANCOVA in PANSS (positive and negative symptoms scale) and CGI-S (clinical global impressions severity) scores compared to placebo. Lurasidone was also found to have negligible effects on lipids, BMI, and HBA1c compared to placebo.<sup>1</sup>



There was an increase in extra-pyramidal symptoms (EPS) when treating with lurasidone. 11% of patients in the 120 mg group and 9.2% in the 40 mg group reported EPS, compared with 4.9% in the olanzapine group and 1.7% in the placebo group. Significant changes in Simpson Angus and Barnes scales for EPS were observed in the 120 mg group, and two patients in the 120 mg group discontinued due to EPS.<sup>1</sup>

The incidence of QTc interval changes for patients treated with lurasidone was comparable to those for patients in the placebo group. Of the 237 patients treated with lurasidone in this study, none had a QTc increase over 60 ms, or a QTc over 500. While one patient had a QTc over 450 ms at baseline, no other patient had QTc over 450. Significance testing of safety parameters was performed by ANCOVA, finding no significant risk of QTc prolongation with lurasidone.<sup>1</sup>

As a randomized controlled trial with blinding, intention to treat analysis, and adequate size, and follow-up, this research is level 1 evidence per the SORT criteria. In conclusion, there is very strong evidence that lurasidone has a negligible risk of QTc prolongation.

This outcome applies well to the patient in terms of illness and ethnicity. Like the subjects in the trial, she has chronic schizophrenia and had recently been hospitalized for an acute exacerbation. The patient's race was well represented in the study, with 30-40% of patients being African American.<sup>1</sup>

The patient is 60 years old, while the mean age of patients in the study was 37. However, she does meet inclusion criteria being between ages 18-75. Furthermore, the patient is female and 77-78% of patients in all treatment groups were male.<sup>1</sup> The predominance of men in the study is understandable given that schizophrenia is more common in males.<sup>6</sup>

Notably, ANCOVA subgroup analyses showed no interactions with gender, race, or age for the PANSS or CGI-S scores<sup>1</sup>, so the efficacy data for lurasidone can be confidently applied to our patient.

## Clinical Application

The research described has substantial benefit in identifying an antipsychotic with negligible risk of prolonging QTc. The patient presented with acute exacerbation of schizophrenia and prolonged QTc. She met the inclusion criteria for the study and per its results could safely be given lurasidone. Lurasidone's potential lack of metabolic effects might also make it a good choice in this patient with obesity.

Lurasidone's relatively high cost as a newer medication can provide a barrier to treatment in some patients. In this case the patient's daughter agreed that lurasidone was the best option to treat her mother, and helped the patient afford the medication. Otherwise, the team may have had to use an older and less expensive medication with low risk of QTc prolongation, such as olanzapine<sup>2</sup>, but the associated metabolic effects would have made this a less desirable choice.<sup>2</sup>

Significant side effects are associated with lurasidone, most notably extrapyramidal syndromes.<sup>1</sup> It remains to be seen whether lurasidone has substantial risk of tardive dyskinesia and studies of longer duration will be needed to assess this.

In summary, lurasidone provides a safe and efficacious alternative to other antipsychotics in patients with prolonged QT interval. Higher risk of extrapyramidal symptoms is a potential drawback.

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