The risk of ventricular dysrhythmia or sudden death in patients receiving serotonin reuptake inhibitors with methadone: A population-based study

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Background

- Drug interactions are a potentially avoidable risk factor for certain complications and are understudied.
- Methadone is a long-acting opioid largely used to treat opioid use disorder. Methadone is a mixture of compounds that are metabolized by different enzymes. (R)-methadone is an opioid agonist while (S)-methadone is associated with abnormal heart rhythms and sudden death. Other medications that interfere with the metabolism of (S)-methadone may increase its concentrations and potentially increase the risk of complications.
- Mental health illness often co-occurs in methadone-treated patients. The likelihood of co-prescribing serotonin reuptake inhibitors (SRIs), the most commonly prescribed antidepressants, with methadone is high.
- Some SRIs have also been found to increase the concentration of (S)-methadone, and others may add to the risk of abnormal heart rhythms by prolonging the QT interval. Yet, the cardiac safety of combining SRIs with methadone is unknown.

What did we investigate?

The risk of abnormal heart rhythms and sudden death in patients receiving methadone and serotonin reuptake inhibitors (SRIs).

How was the study conducted?

Design: Nested case-control study.

Population: Ontario residents receiving methadone maintenance therapy.

Study period: Between April 1996 and December 2017.

Case: Patients who died of sudden cardiac death or were hospitalized with ventricular dysrhythmia (abnormal heart rhythms) or cardiac arrest on the day of or within one day after receiving a prescription for methadone.

Control: Patients who also received methadone matched to the cases on age, sex, and/or a disease risk score.

Exposure: Prescriptions for SRIs (citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline) within 90 days of hospitalization or death.

Analysis: Odds ratio (OR) and p-value functions for the association between methadone-related cardiotoxicity and treatment with SRIs known to inhibit the metabolism of (S)-methadone or prolong the QT interval.

Key findings

- Certain SRIs may be associated with a small increase in cardiac toxicity in patients receiving methadone.
- The drug interaction between methadone and commonly-prescribed SRIs is a potential contributing cause in the occurrence of cardiac toxicity among patients receiving methadone, particularly those with no pre-existing cardiac risk factors.

What did we find?

- During the 21-year study period, 626 patients receiving methadone who died of sudden death or were hospitalized for abnormal heart rhythms were matched to at least one control.
- Case patients had greater co-morbidity, received more prescription drugs, and had more visits with a cardiologist in the year prior.
- SRIs were associated with a 30% (sertraline, fluvoxamine or paroxetine) and 26% (citalopram and escitalopram) increased risk of cardiac toxicity in patients receiving methadone.

Recommendations for clinicians

- Clinicians should follow standard methadone monitoring practices to reduce the risk of combined methadone-SRI therapy, including identification and management of risk factors for abnormal heart rhythms, pre-treatment and follow-up electrocardiographic (ECG) monitoring.
- If clinically appropriate, selection of an antidepressant that does not interact with methadone is suggested.

For more information

Antoniou, T., McCormack, D., Tadrous, M., Juurlink, D. & Gomes, T. (2022). The risk of ventricular dysrhythmia or sudden death in patients receiving serotonin reuptake inhibitors with methadone: A population-based study. *Frontiers in Pharmacology.*

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