CHANGES IN QTc INTERVAL DURATION AMONG HEROIN ADDICTS ON METHADONE TREATMENT

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PROMENE U TRAJANJU QTc INTERVALA KOD HEROINSKIH ZAVISNIKA NA METADONKOM TRETMANU

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ABSTRACT

This paper aimed to collect and unite facts known about the effect of methadone treatment on QTc interval prolongation that could determine precipitating factors in the development of heart arrhythmias and their consequences (Torsade de Pointes and sudden cardiac death), and to raise the methadone treatment safety level.

Studies conducted up to now clearly demonstrate that methadone therapy evokes changes in the heart's electrical conduction, but those studies also show that QTc interval prolongation could be precipitated by other factors. The most often present risk factors in our research were dose of methadone, co-medication, and co-morbidity, but other relevant risk factors were gender, age, misuse of illicit drugs, therapy length and tobacco use.

Active participation in modern treatment processes and implementation of knowledge acquired recently into daily practice, such as setting up reutilized questionnaires and diagnostic methods to expose higher risk for complications and providing broader therapeutic range for cases of drug replacement necessity, will enhance therapy safety level and bring us to the next step of resocialization of these patients, which needs to remain the final goal of treatment.

Keywords: methadone treatment, QTc interval prolongation, Torsade de Pointes, sudden cardiac death

SAŽETAK

Cilj ovog preglednog članka je da prikupi i objedini do sada poznate činjenice, o efektima metadonske terapije na produženje QTc intervala, koje mogu da ukažu na predisponirajuće faktore za nastanak srčanih aritmija i njihovih posledica (Torsade de Pointes, iznenadna srčana smrt) kao i da unaprede sigurnost prilikom upotrebe ove terapije. Studije sprovedene do sada definitivno pokazuju da terapija metadonom izaziva promene u električnoj provodljivosti srca, ali i da produženje QTc intervala može da bude uslovljeno i drugim faktorima. U najčešće faktore rizika se ubrajaju doza metadona, udružena terapija, ko-morbiditet, pol, starost, zloupotreba ilegalnih droga, dužina terapije i konzumiranje duvana. Aktivno učešće u modernim terapijskim procedurama i uključivanje do sada stečenih znanja u rutinsku praksu (putem uvođenja upitnika i dijagnostičkih metoda) radi utvrđivanja rizika za nastanak komplikacija i obezbeđivanja šireg terapijskog spectra, će podići nivo sigurnosti prilikom upotrebe lekova i dovesti nas do sledećeg koraka – resocijalizacije pacijenata, što treba da ostane krajnji cilj terapije.

Ključne reči: terapija metadonom, produženje QTc intervala, Torsade de Pointes, iznenadna srčana smrt

INTRODUCTION

Methadone is the most commonly used drug in opioid maintenance treatment, and it has been on the WHO's list of essential medicines since 2005 (1); however, it was also noted by the FDA in 2006 as a drug with serious side effects, such as respiratory centre depression and cardiac dysrhythmia (2). The assumption is that methadone causes cardiac dysrhythmia by prolonging QTc interval, which is a risk for Torsade de Pointes that could evolve into sudden cardiac death.

Although methadone therapy has been used for over 40 years to treat opioid addiction, its side effects were first seriously indicated in 2006 (2), when numerous studies were published. However, there was no adequate experimental clinical study (3). A lack of controlled randomized studies with a placebo group was justified by the specific characteristics of this disease and the necessity for constant therapy. Meanwhile, in recent years, important compara-

tive experimental studies have been published with results demonstrating new approaches towards the abovementioned problems.

The main questions on this topic are as follows: does methadone cause prolongation of QT interval, does methadone prolong QT interval enough to cause ventricular tachycardia, and is QT interval length subject to other factors present among these patients?

This review aimed to both summarize previous knowledge on this topic and to note the newest research in comparative and other clinical studies and thus consolidate knowledge in the area of methadone maintenance treatment (MMT) to improve the safety of patients receiving therapy for heroin addiction.

Methadone

Methadone, a synthetic agonist of mu receptors, is administered orally for the treatment of opioid addiction, and it is most often used as a racemic mixture of R- and S-enantiomers. Whereas R-enantiomer mostly causes an opioid effect (4), both R- and S-enantiomers function like an antagonist of N-methyl-D-aspartic acid (NMDA) (5). Oral bioavailability of methadone is 70-90%, and it is transported bound to plasma proteins (6). It is metabolized in the liver by the cytochrome P450 enzyme system - mainly by CYP3A4 and CYP2B6 - whose activities are genetically and environmentally determined (7). It is important to note the stereo selectivity of the CYP2B6 enzyme towards S-methadone, which has been shown in vitro (8) and confirmed in vivo by showing that this enzyme is a slower metabolizer of methadone and thus produces higher S-methadone serum levels in people with the CYP2B6 genotype (9). Additionally, there are certain drugs that are metabolized by or inhibit these enzymes that may increase plasma methadone levels (10).

The most effective dosage of methadone for opioid dependence treatment is 60-100 mg per day (11).

QT Interval

The length of the QT interval, which is the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle, is predictive of Torsade de Pointes, which can be fatal (12). QT interval is corrected by Bazett's formula (QTc) because it is dependent on the heart rate (13). Normal QTc interval is considered <430 ms in men and <450 ms in women, whereas a prolonged QTc interval has been defined as >450 ms for men and >470 ms for women (14). TdP will not follow every QTc interval prolongation, but QTc prolongation over 500 ms significantly increases the risk of TdP (15).

Studies on congenital long QT syndrome have provided an underlying reason for QT prolongation. Numerous mutations of the KCNH2 gene that code the human ether-a'-gogo related gene (hERG) voltage-gated potassium channel in the human heart are responsible for congeni-

tal long QT syndrome and sudden death caused by malignant ventricular arrhythmias (16). The importance of these channels among OMT patients became clearer (17) when it was shown that hERG channels might be blocked by some drugs, like methadone (18).

METHODS

We searched the PubMed database using the following key words: *Methadone maintenance treatment, and QTc prolongation with the following filters: Publication date from 1980/01/01 to 2013/01/01, Clinical Trial, Randomized Controlled Trial, Humans and English*. We obtained 4 search results.

In order to complete our research, we obtained additionally used research papers connected to results from our basic search (Related citations in PubMed) that were offered together with the results from the basic search.

Not all of the results obtained this way fit within our topic of interest, so our research team divided into four groups that independently reviewed gathered research papers to identify common parameters to select the research papers of interest. Included parameters were *Methadone maintenance treatment* and *QTc prolongation* as the topic of the research papers.

After an independent review of the research papers, all 4 groups held a meeting, excluded research papers that appeared in more than one group, and once more reviewed the rest of the research papers with the aim of determining that they all included the appropriate parameters. This method brought us a satisfactory number of research papers and increased the amount of literature to be used as source of information on this topic.

Another limitation we faced at this stage was that a great number of research papers obtained through the PubMed database contained only abstracts. We tried to overcome this by sending appeals to the authors of these papers asking for the full research paper for the review to be as complete as possible. In this way, we gained full access to the majority of the research papers.

Additionally, research papers that were not in our PubMed database search but were accessible to team members were used as information sources but will be not found in the RESULTS section because they were not the result of PubMed database search.

RESULTS

Experimental studies

In 2008, Wieneke et al. published a randomized, controlled clinical trial that compared LAAM with methadone (19). The methadone group consisted of patients on MMT for at least one month and with a stable methadone dosage (less than 100 mg/day) for at least two

weeks. Exclusion criteria were used to form groups of patients without cardiac disease, serious psychiatric diseases or somatic disorders and with negative urine drug screen for opiates during the screening period. After 4 weeks of methadone therapy, patients were randomized into two groups (group treated with LAAM and group treated with methadone) and followed for 24 more weeks. For the purpose of this review, only the methadone group is described. The 22 patients in the methadone group had a mean age of 31 years. Twelve patients were women. The mean methadone dose before randomization was 72.0 ± 25.5 mg/day compared to 69 ± 27.6 mg/day in the next phase. This study did not show significant changes in QTc interval, which varied from $406 \text{ ms} \pm 29 \text{ ms}$ at the beginning to $405 \text{ ms} \pm 25 \text{ ms}$ after 24 weeks.

Another study compared different medicines in the treatment of heroin addiction (20). An advantage of the study performed by Wedam et al. was its design, a randomized, double-blinded study, but it lacked a placebo group for ethical reasons. At the beginning of the study, the mean QTc interval was 412.6 ms, and after 16 weeks, the mean QTc interval increased to 446.9 ms. Among 53 participants in the methadone group, 23 % had QTc intervals longer than 470 ms for males and 490 ms for females, and 6 participants in the study developed QTc interval values over 500 ms. It is important to mention that 12 % of participants had QTc intervals that lengthened by more than 60 ms compared with baseline values. The methadone dose used varied from 60 to 100 mg.

Observational studies

In 2008, Krantz conducted a prospective cohort study with 151 participants with the aim to evaluate the influence of methadone on QTc interval length (21). After selecting the participants, a baseline ECG was performed followed by a second ECG after 6 months. The results showed that QTc interval prolongation was present among 76% of patients on methadone, whereas the rest of the patients did not have prolongation or the QTc interval length was shortened. Specifically, QTc intervals over 450 ms were found among 7% of patients at the baseline ECG and among 19% after 6 months. A QTc interval over 470 ms was present in 3% of patients at the first ECG and in 7% at the second ECG. There was no case of a QTc interval longer than 500 ms at the baseline ECG, but this value was exceeded in 2% of patients after 6 months of study. None of the patients developed TdP during the study. The practical implications of the study were a non-significant prolongation of the QTc interval of less than 30 ms among 18% of participants, but a clinically more significant prolongation of more than 60 ms compared to the baseline ECG was present among 3% of patients.

Another prospective study performed by Krantz et al. gathered 118 newly recruited patients of an MMT program who started therapy with a 30 mg daily methadone dose that was afterwards adjusted based on information

about previous heroin use, clinical assessment of withdrawal symptoms, and illicit opiate usage proved by urine analysis (22). Baseline QTc values varied from 367 to 483 ms (mean value 415.3 ms) but increased to 376 - 533 ms (mean value 429.4 ms) after 6 months. As the upper limit of normal QTc values was considered 430 ms for males and 450 ms for females, this resulted in QTc interval prolongation among 14% of patients at the beginning of the study and 31% at the end. The methadone doses used varied from 20-180 mg per day. However, Martel et al. continued the study and added an ECG performed after 12 months from the beginning of the study (23). The difference was that for this study, the upper limit of the normal QTc values was set 450 ms for men and 470 ms for women. Under these conditions, just 3% of patients had prolonged QTc values at the baseline ECG and 24% had prolonged QTc values after 6 months. At the end of the study, 22% had prolonged QTc values, and 2 participants had QTc values over 500 ms (23).

A study with 83 patients who were on MMT for longer than 6 months with a steady maintenance daily dose and with methadone as the only used medication showed 2 patients with QTc intervals longer than 500 ms, but neither patient had ever experienced symptoms of a heart disorder (24). Maremmani et al. found 69 patients (83.1%) with prolonged QTc intervals beyond the upper limits of normal QTc values of 440 ms in males and 460 ms in females. Patients did not have an electrolyte imbalance and had a negative urine test for cocaine, morphine and amphetamines. The researchers concluded that there was an absence of proof that methadone had no effect on cardiac function, but they did not find any correlation between QTc length and methadone dose. Additionally, due to the fact that there were only two cases of QTc intervals longer than 500 ms, they speculated that there was no risk of arrhythmia among MMT patients as long as methadone was administered as the only therapy.

Mayet with a group of scientists conducted a cross-sectional study on the prevalence of QT prolongation among patients on MMT and the appearance of TdP (25). The study group consisted of patients who fulfilled the criteria proposed by The Medicines and Healthcare Products Regulatory Agency (patients on methadone with heart/liver disease, electrolyte abnormalities, concomitant QT prolonging medications/CYP3A4 inhibitors or prescribed methadone >100 mg daily) (26). This research showed that the prevalence of QTc prolongation (>450 ms for males and >470 ms for females) was 18.1%, whereas there was neither QTc prolongation over 500 ms nor the occurrence of TdP.

Researchers from France followed a group of 42 outpatients by measuring the QTc interval during their visits to the centre for treatment of addiction diseases. Independently, they searched through the French pharmacovigilance medical reports database dating from 1996 to 2007 and singled out reports of cardiac symptoms connected to methadone treatment. The results of both studies were published separately (27). They recorded data on co-med-

ication, comorbidity, electrolyte status, and psychoactive substance abuse. The study started with 100 patients, although an ECG was obtained from only 42 patients, and showed QTc interval prolongation among 4 patients with a maximal prolongation of 36 ms compared to the reference values.

Another cross-sectional study followed patients on medication treatment for addiction with the aim to define the prevalence of QTc prolongation. This study collected data from a registry of all patients on medication treatment for addiction in Norway from 1997 to 2003 for the purpose of discovering mortality that was potentially caused by therapy (28). The cross-sectional study involved 173 patients treated with methadone, and among them, 4.6% ($n = 8$) had a QTc interval above 500 milliseconds, 15% ($n = 26$) had a QTc interval above 470 milliseconds, and 28.9% ($n = 50$) had a QTc interval above 450 milliseconds.

Another study included 138 patients who were on treatment for at least 100 days and on a stable methadone dose for at least 14 days as well as 111 (80.4%) patients who received more than 120 mg/day of methadone. This study measured methadone serum levels and QTc interval (29) and reported several comorbidities, 76 patients were positive for HCV and 11 were positive for HIV, as well as drug abuse. The results showed only 3 patients with QTc intervals longer than 500 ms (upper limit of normal and clinically relevant in this study) and found no correlation between QTc interval and methadone doses and serum levels. This study did find a significant correlation between methadone dose and QTc interval among 31 patients with urine positive for cocaine, but did not find a significant correlation among patients abusing other drugs (e.g., benzodiazepine, opiate, cannabis, amphetamine).

The cross-sectional study conducted by Eap et al. found 9% of patients with QTc prolongation among 179 patients on methadone treatment (30). All of the QTc prolongations occurred in men. Patients were on MMT for at least 6 months at the time when the study was conducted, with the exception of 9 participants with the lowest duration of treatment being 2 months. Methadone plasma concentrations were in steady state in all except one patient.

The studies that provided the most detailed data for patients on methadone treatment were clinical cases. Although these studies do not provide statistical values, they clearly show an interaction between methadone dosage, risk factors, and QTc values.

A clinical case of a 52-year-old, HIV+, female patient without previous cardiologic problems but with prolonged QTc interval and occurrence of TdP after a high dose of methadone was described by Denise D. Routhier et al. (31), suggesting the ability of methadone to induce QTc prolongation and Torsade de Pointes. Additional data showed that this patient arrived at the hospital with hypokalaemia and hypomagnesaemia even though the serum K^+ and Mg^{++} concentrations were normal at the time of the arrest. Additionally, a urine drug screen was positive for cocaine and benzodiazepines as well as other medications, among

them alprazolam, which shares in CYP3A4 metabolism. The patient was diagnosed with hepatitis B and C, but the liver function was good. Daily dosage of methadone was 145 mg, and when gradually reduced to 80 mg, QTc interval narrowed from 618 ms to 503 ms on hospital day 4 and to 454 ms on day 19, at the time of discharge. Another group of scientists from the University of Pittsburgh wrote a case report on this patient, concluding that TdP occurred due to its multifactorial aetiology (32).

Another case series presented 4 patients with prolonged QTc interval and arrhythmias while on high doses of methadone (33). Here, there were also other risk factors such as hypokalaemia (among 3 patients), co-medication, abuse of illicit substances and structural heart disease. Although the authors stated that methadone treatment was continued in all 4 cases and that QTc interval was normalized and arrhythmias vanished when risk factors were suppressed, they concluded that methadone should be on the list of drugs that can produce QTc interval prolongation and TdP.

DISCUSSION

After our literature search, we need to mention couple of limitations in the research on methadone maintenance treatment programs. The biggest limitation is a lack of experimental clinical trials with placebo groups, which are impossible for ethical reasons. Other limitations are connected to the specific behaviour of patients. Almost every study faced the problem of patients ending participation in the research.

However, in recent years, progress has been made, and a couple of experimental clinical studies that compared the effect of methadone and other medications in opioid dependence treatment have been published. Additionally, new insight into the effect of methadone on QTc interval was given by in vitro studies that tested the consequences of different genotypes on QTc interval.

Does methadone therapy lead to QTc interval prolongation among MMT patients? It was impossible to systematically analyse study results using only one reference value (Table 1). The most often used reference values for QTc were the ones proposed by the Committee for Proprietary Medicinal Products (CPMP) (14). Nevertheless, many authors used different reference values (20-29), which made it impossible to produce comprehensive results using the given data. Some authors preferred to measure QTc prolongation as an absolute increase in QTc. (20, 21, 22). According to the International Conference on Harmonization, absolute increases greater than 30 ms and greater than 60 ms are important (34), which is a good way to describe the influence of methadone on QTc interval at baseline values. However, despite all the problems mentioned above, there were patients on methadone maintenance programs with prolongation in QTc interval.

Table 1: References used for interpretation of QTc values.

Name of the study	Reference	Values
QT interval prolongation: prevalence, risk factors and pharmacovigilance data among methadone-treated patients in France. <i>Perrin-Terrin A, Pathak A, Lapeyre-Mestre M.</i>	Reference not stated	3 (7.1%) >450 ms for males 0 >470 ms for females ¹
Methadone maintenance, QTc and torsade de pointes: who needs an electrocardiogram and what is the prevalence of QTc prolongation? <i>Mayet S, Gossop M, Lintzeris N, Markides V, Strang J.</i>	Moss AJ. Measurement of the QT interval and the risk associated with QTc interval prolongation: a review. <i>Am J Cardiol</i> 1993;72:23B–5B.	13 (15.7%) ≥450 ms for males 2 (2.4%) ≥470 ms for females
Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. <i>Anchersen K, Clausen T, Gossop M, Hansteen V, Waal H.</i>	Krantz M. J. Heterogeneous impact of methadone on the QTc interval: what are the clinical implications? <i>J Addict Dis</i> 2008; 27: 5–9.	85 (49.1%) >430 ms 50 (28.9%) >450 ms 26 (15%) >470 ms 8 (4.6%) >500 ms
Heterogeneous impact of methadone on the QTc interval: what are the practical implications? <i>Krantz MJ</i>	Author set reference values	62 (41%) >430 ms 29 (19%) >450 ms 11 (7%) >470 ms 3 (2%) >500
Corrected-QT intervals as related to methadone dose and serum level in methadone maintenance treatment (MMT) patients: a cross-sectional study. <i>Peles E, Bodner G, Kreek MJ, Rados V, Adelson M.</i>	Moss A. J., Zareba W., Benhorin J., Couderc J. P., Kennedy H., Locati-Heilbron E. et al. ISHNE guidelines for electrocardiographic evaluation of drug-related QT prolongation and other alterations in ventricular repolarization: task force summary. A report of the Task Force of the International Society for Holter and Noninvasive Electrocardiology (ISHNE), Committee on Ventricular Repolarization. <i>Ann Noninvasive Electrocardiol</i> 2001; 6: 333–41.	12 (7.9%) ≥450 ms 7 (4.6%) 500 > QTc ≥460 ms 3 (2%) >500 ms
QTc interval prolongation in patients on long-term methadone maintenance therapy. <i>Maremmani I, Pacini M, Cesaroni C, Lovrecic M, Perugi G, Tagliamonte A.</i>	Vincent GM, Timothy K, Leppert M, Keating M: The spectrum of symptoms and QT interval in carriers of the gene for the long-QT syndrome. <i>N Engl J Med</i> 1992; 327:846–852.	2 (2.4%) >470 ms for males 0 >480 ms for females
Levo-alpha-acetylmethadol (LAAM) induced QTc-prolongation - results from a controlled clinical trial. Wieneke H, Conrads H, Wolstein J, Breuckmann F, Gastpar M, Erbel R, Scherbaum N.	Committee for Proprietary Medicinal Products (CPMP). Points to consider: the assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. The European Agency for the Evaluation of Medicinal Products. December 1997 [CPMP/986/96].	1 (4.5%) 431 – 450 for males and 451 – 470 for females
QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. <i>Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MC.</i>	Author's modification of thresholds for abnormal prolongation of the QTc	13 (23%) >470 ms for males >490 ms for females
Effects of methadone on QT-interval dispersion. <i>Krantz MJ, Lowery CM, Martell BA, Gourevitch MN, Arnsten JH</i>	Garson A Jr. How to measure the QT interval: what is normal? <i>Am J Cardiol</i> 1993;72:14B–16.	19 (16%) >430 for ms males >450 ms for females
Impact of methadone treatment on cardiac repolarization and conduction in opioid users. <i>Martell BA, Arnsten JH, Krantz MJ, Gourevitch MN</i>	Authors defined a prolonged QTc interval as >450 ms for man and >470 ms for women without stating reference.	14 (20% of man 2% of women) >450 ms for man >470 ms for females
Stereoselective Block of hERG Channel by (S)-Methadone and QT Interval Prolongation in CYP2B6 Slow Metabolizers <i>CB Eap, S Crettol, J-S Rougier, J Schlaepfer, L Sintra Grilo, J-J De'glon, J Besson, M Croquette-Krokar, P-A Carrupt and H Abriel</i>	European Agency for the Evaluation of Medicinal Products. Committee for Proprietary Medicinal Products. The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. CPMP/986/96. http://www.emea.eu.int/pdfs/human/swp/098696en.pdf (1997).	42 (26%) 430<QTc<450 16 (9%) >450 for males >470 for females

Does methadone prolong QTc interval enough to evoke ventricular tachycardia? The point that all the researchers agreed upon was the importance of QTc prolongation over 500 ms. Our research identified four studies that reported

patients who did not have QTc intervals exceeding 500 ms (19, 22, 25, 27), but in one study, 6 of the 52 patients did have a QTc interval over 500 ms at some point in the study (20). Even though researchers have agreed that a QTc in-

interval exceeding 500 ms is an important threshold, there were no cases of TdP. A possible explanation could be the fact that for registering events as rare as TdP, much larger study groups are necessary than the ones usually formed in MMT research studies (35). The largest study group we reviewed had 179 patients (30). Studies in our research that provided any data on TdP were clinical cases (31-33). All the studies with TdP events and data on QTc length found that in these clinical cases, TdP occurred among patients with a QTc interval over 600 ms (31, 32).

Does the existence of other factors present among these patients have an effect on QTc interval length? Even though TdP appeared only among patients with QTc values significantly over the threshold known to be high risk for developing TdP, all of these patients also had 2 or more risk factors (31-33). The most often present risk factors in our research were dose of methadone (23, 25, 27, 28, 29, 30), co-medication (22, 23, 27, 30), and co-morbidity (22, 23, 27), but also present were gender (23, 24, 28), age (23, 28), misuse of illicit drugs (25, 29), therapy length (28, 29), and tobacco use (27).

The influence of methadone dose on QTc interval length was statistically demonstrated by uni- and multivariate analysis in certain studies from our research (table 2). The dose range in all of the studies from our research was 5-600 mg/day, whereas the most effective opioid dependence treatment dosage of methadone is 60-100 mg/day (11). According to the Medicines and Health Care products Regulatory Agency (MHRA), a high dosage is considered anything above 100 mg/day (26). Studies that gave detailed data on the dosage of methadone showed that all cases of QTc prolongation over 500 ms, except one (24), were receiving more than 100 mg/day of methadone (24, 28, 29).

The often-present co-morbidities among MMT patients lead to considerable co-medication. HIV and HCV infections lead to electrolyte imbalance and to acute hepatitis that reduces the efficacy of methadone-metabolizing enzymes. Concomitant use of medicines that directly affect QTc interval or indirectly by interaction with methadone-metabolizing enzymes, thus increasing serum methadone level, could affect the length of QTc prolongation. A list of medicines that interact with MMT can be found online (35).

The reviewed data undoubtedly show the presence of prolonged QTc interval among some MMT patients, but it is hard to define how much of this QTc prolongation is the result of methadone activity and how much is the effect of other risk factors. Eap et al. pointed out that the presence of co-medication was similar between groups of patients with and without QTc prolongation, although uni- and multivariate analysis in their study showed a correlation between co-medication and QTc interval prolongation (30). An explanation for this could be found in the results of the latest genetic studies that showed inter-individual variations in the methadone metabolizing process and structure of cardiac ion channels (30, 36). A group of scientists led by Prof. Eap and coworkers researched stereo selectivity of methadone-induced hERG channel blockage, and at the same time, they

tested the hypothesis that CYP2B6 slow metabolizer status was connected with prolonged QTc interval (30). Out of 179 patients included in this study, 6% had the CYP2B6 slow metabolizer genotype. The results of the study showed longer QTc intervals and higher plasma S-methadone concentrations in people with the CYP2B6 slow metabolizer genotype (439 $\pm$ 25 ms VS 421 $\pm$ 25 ms), whereas concentrations of plasma R-methadone were the same among all the patients. Higher incidence of borderline and prolonged QTc intervals (>450 ms) among patients with the CYP2B6 slow metabolizer genotype were also found. Prolonged QTc interval was noted among 3 of the 11 patients with this genotype (27%), whereas QTc prolongation among patients with other genotypes was noted in 13 out of 168 cases (8%). If we take into account borderline and prolonged QTc intervals, both parameters were found in 8 out of 11 patients with the CYP2B6 slow metabolizer genotype (73%), and 50 out of 168 patients with other genotypes.

Another genetic study tested mutations on five genes that coded for subunits of cardiac ion channels among OMT patients identified with QTc > 500 ms (36). Out of 200 patients, 8 were recruited, and genetic testing revealed two heterozygous mutations for long QT syndrome (LQTS). The authors speculated that phenotypically silent or subclinical LQTS mutation carriers may become symptomatic in the presence of other risk factors. As LQTS carrier status is often unknown to the individual and clinician prior to the risk exposure, it could be directly manifested by syncopal and cardiac arrest episodes as had happened with these two patients from the study. During this study, 24-h ECG recordings were performed and showed diurnal fluctuations of the QTc interval in all patients; thus, the authors concluded that because of diurnal fluctuations of the QTc interval, there might have been missed cases of LQTS mutations among the rest of the patients who had a QTc < 500 ms in the assessment study.

The authors of both studies presented data on the frequency of these genetic mutations (6% of Caucasians with CYP2B6 SM status and prevalence of between 1/100 and 1/300 of heterozygous mutation carriers in the general population), stating that these genotypes are of clinical relevance for methadone treatment.

To increase the safety of patients on MMT, the authors recommend that physicians obtain a careful screen for risk factors associated with long QT syndrome (23, 24, 31, 32), cardiac evaluation and systematic ECG especially among patients with a medical history of cardiac diseases, presence of congenital long QT syndrome and sudden cardiac death in families, a methadone dosage greater than 120 mg (28) and after changes in therapy regime (27). They also mention that methadone's more favourable cost profile and efficacy will still keep it as a first line of opiate addiction treatment (22, 24, 30).

Undoubtedly, improvement in the resocialization process as a final step of opiate addiction treatment leads to a reduction in methadone dose and finally exclusion from methadone treatment, thus erasing any potential effect of methadone on QTc interval.

Table 2: Research papers that shows statistically significant risk factors.

Effects of methadone on QT-interval dispersion. <i>Krantz MJ, Lowery CM, Martell BA, Gourevitch MN, Arnsten JH.</i>	UNIVARIATE ANALYSIS	Baseline clinical variables tested for association with QT dispersion were age, sex, taking drugs that affect cardiac repolarization or methadone metabolism, self-reported cardiovascular disease, use of cocaine at baseline, and infection with human immunodeficiency virus or hepatitis C. Of these variables, the only one associated with the magnitude of QT dispersion at baseline was self-reported cardiovascular disease (42.1 vs 31.7 msec, $p < 0.01$). At 6 months none of these variables remained significantly associated with absolute QT dispersion. The same clinical variables were then tested for association with the magnitude of change in QT dispersion over 6 months and only concurrent antidepressant therapy was associated with a greater increase in QT dispersion (20 vs 8.5 msec, $p = 0.04$).
	BIVARIATE ANALYSIS	N/A
	MULTIVARIATE ANALYSIS	N/A
	STATISTICAL TEST USED	Univariate associations were tested using Pearson correlation coefficients for continuous independent variables and the Student t test for categorical independent variables. Multivariate associations with the magnitude of the change in QTc interval were tested using linear regression models.
Impact of methadone treatment on cardiac repolarization and conduction in opioid users. <i>Martell BA, Arnsten JH, Krantz MJ, Gourevitch MN</i>	UNIVARIATE ANALYSIS	Variables associated with a longer QTc interval at baseline were older age ($r = 0.25$, $p = 0.001$), female gender (women vs men, 426 vs 414 ms; $p = 0.001$), self-reported cardiac disease (434 vs 416 ms, $p = 0.03$); use of antidepressants (430 vs 418 ms, $p < 0.0001$) and calcium antagonists (432 vs 417 ms, $p = 0.07$); hepatitis C infection (423 vs 413 ms, $p = 0.08$) and HIV infection (423 vs 417 ms, $p = 0.08$). Only the methadone dose was significantly associated with the magnitude of the QTc increase from baseline to 6 months ($r = 0.18$, $p = 0.03$).
	BIVARIATE ANALYSIS	N/A
	MULTIVARIATE ANALYSIS	Controlling for all factors associated with the baseline QTc interval and use of heroin, cocaine, and/or benzodiazepines, factors that were associated with greater QTc prolongation from baseline to 6 months, included male gender, HIV infection, and methadone dose. At the 12-month follow-up only the 12-month methadone dose remained marginally associated with the magnitude of the QTc increase ($p = 0.08$).
	STATISTICAL TEST USED	Univariate associations were tested using Pearson's correlation coefficients for continuous variables and the Student t test for categorical variables. Multivariate associations with the magnitude of the QTc interval or change in QTc interval were tested using linear regression models with $p < 0.10$ as the model entry criterion.
QT interval prolongation: prevalence, risk factors and pharmacovigilance data among methadone-treated patients in France. <i>Perrin-Terrin A, Pathak A, Lapeyre-Mestre M.</i>	UNIVARIATE ANALYSIS	N/A
	BIVARIATE ANALYSIS	N/A
	MULTIVARIATE ANALYSIS	In the multiple linear regression, QTc length was associated ($r^2 = 0.74$) with history of heart disease [$b = 251.3$ (SD 123.4), $P = 0.04$], tobacco use [$b = 234.5$ (SD 74.9), $P = 0.003$], and QT-prolonging drugs [$b = 275.5$ (SD 78.2), $P = 0.001$]. QT dispersion was associated ($r^2 = 0.73$) with history of heart disease [$b = 62.8$ (SD 26.6), $P = 0.02$], recent increase in methadone dose [$b = 68.5$ (SD 21.6), $P = 0.003$], tobacco use [$b = 50.1$ (SD 16.1), $P = 0.003$], and QT-prolonging drugs [$b = 60.8$ (SD 74.9), $P < 0.001$].
	STATISTICAL TEST USED	Multiple linear regression
Methadone maintenance, QTc and torsade de pointes: who needs an electrocardiogram and what is the prevalence of QTc prolongation? <i>Mayet S, Gossop M, Lintzeris N, Markides V, Strang J.</i>	UNIVARIATE ANALYSIS	N/A
	BIVARIATE ANALYSIS	Bivariate analysis found no factor independently associated with QT length or QTc prolongation.
	MULTIVARIATE ANALYSIS	Multivariate analysis, via multiple linear backward regression, investigated the relationship between QTc length and the following covariates: prescribed methadone daily dose (log base 10), stimulant use (illicit and prescribed), benzodiazepine use (illicit and prescribed), alcohol use, heroin use, tobacco use, cannabis use, gender and age. Total daily methadone dose ($b = 0.318$, $P = 0.003$) and use of stimulants (cocaine or amphetamines) ($b = 0.213$, $P = 0.043$) were found to be predictive of QTc length. Binary logistic regression was conducted investigating QTc prolongation did not reveal a statistically significant association.
	STATISTICAL TEST USED	Multiple linear backward regression
Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. <i>Anchersen K, Clausen T, Gossop M, Hansteen V, Waal H.</i>	UNIVARIATE ANALYSIS	Dose of methadone (0.373*) $P = 0.001$ $b = 0.365$ Gender (0.080*) $P = 0.295$ $b = 0.079$ Age (years) (0.134*) $P = 0.080$ $b = 0.115$ Time in treatment (0.144*) $P = 0.058$ $b = 0.027$
	BIVARIATE ANALYSIS	N/A
	MULTIVARIATE ANALYSIS	Dose of methadone $B 0.367^{**}$ 95% CI of $B 0.22 - 0.51$ $P = 0.001$ Gender $B 5.988^{**}$ 95% CI of $B -4.62 - 16.59$ $P = 0.226$ Age (years) $B 0.569^{**}$ 95% CI of $B -0.14 - 1.38$ $P = 0.137$ Time in treatment $B 0.029^{**}$ 95% CI of $B -0.14 - 0.20$ $P = 0.410$
	STATISTICAL TEST USED	Pearson's correlation* Multiple linear regression** A positive correlation was found between QTc interval and dose of methadone, both in Pearson's correlation ($r = 0.37$, $P = 0.01$) and in the multiple linear regression analysis ($B = 0.37$, $P = 0.01$). No statistically significant correlation was detected between QTc interval and time in treatment, age or gender

<p>Corrected-QT intervals as related to methadone dose and serum level in methadone maintenance treatment (MMT) patients: a cross-sectional study.</p> <p><i>Peles E, Bodner G, Kreek MJ, Rados V, Adelson M.</i></p>	UNIVARIATE ANALYSIS	N/A
	BIVARIATE ANALYSIS	N/A
	MULTIVARIATE ANALYSIS	QTc correlated significantly with duration in MMT ($r = 0.24$, $P = 0.005$), but only as a trend with methadone daily doses ($r = 0.13$, $P = 0.1$), and not at all with serum methadone levels ($r = 0.01$, $P = 1$). QTc intervals correlated significantly with methadone doses in cocaine abuse patients ($n = 31$), $r = 0.4$, $P = 0.03$), but not in the 107 'non-cocaine-abuse' patients ($r = 0.04$, $P = 0.4$).
	STATISTICAL TEST USED	The correlation between QTc interval and methadone (dose and duration) was determined using Pearson's correlation coefficients. Continuous variables of differences between groups were analyzed using oneway analysis of variance (ANOVA) and results are presented as mean standard deviation. Categorical variables were presented as proportions (%).
<p>QTc interval prolongation in patients on long-term methadone maintenance therapy. (1.14)</p> <p><i>Maremmani I, Pacini M, Cesaroni C, Lovrecic M, Perugi G, Tagliamonte A.</i></p>	UNIVARIATE ANALYSIS	No correlation was found between QTc values and methadone doses or gender.
	BIVARIATE ANALYSIS	N/A
	MULTIVARIATE ANALYSIS	N/A
	STATISTICAL TEST USED	Pearson's correlation
<p>Stereoselective Block of hERG Channel by (S)-Methadone and QT Interval Prolongation in CYP2B6 Slow Metabolizers</p> <p><i>CB Eap, S Crettol, J-S Rougier, J Schlaepfer, L Sintra Grilo, J-J De'glon, J Besson, M Croquette-Krokar, P-A Carrupt and H Abriel</i></p>	UNIVARIATE ANALYSIS	Univariate analysis between QTc interval at trough and several risk factors indicated that trough (R,S)- methadone concentrations ($r = 0.31$, $r^2 = 0.097$, $P = 0.00005$), use of co-medications ($r = 0.18$, $r^2 = 0.034$, $P = 0.01$), methadone daily dose ($r = 0.19$, $r^2 = 0.036$, $P = 0.01$), CYP2B6 SM status ($r = 0.18$, $r^2 = 0.032$, $P = 0.02$), and serum calcium ($r = -0.15$, $r^2 = 0.023$, $P = 0.04$), were predictive of the QTc interval duration. Other variables, such as gender ($P = 0.35$), age ($P = 0.28$), serum potassium ($P = 0.42$), cocaine ($P = 0.45$) and alcohol ($P = 0.51$) consumption, were not predictive of the QTc interval duration.
	BIVARIATE ANALYSIS	N/A
	MULTIVARIATE ANALYSIS	Multivariate analysis yielded a model including trough (R,S)-methadone concentrations ($P < 0.0005$), hypocalcemia ($<2.2\text{mmol/l}$; $P = 0.02$), use of co-medication ($P = 0.03$), and CYP2B6 status ($P = 0.05$) with a determination coefficient (r^2) of 0.17 ($n = 179$; $P = 0.00005$).
	STATISTICAL TEST USED	Pearson correlation, regression, χ^2

Table 3: List of all researches from Results.

<p>QT interval prolongation: prevalence, risk factors and pharmacovigilance data among methadone-treated patients in France.</p> <p><i>Perrin-Terrin A, Pathak A, Lapeyre-Mestre M.</i></p>	Journal	Fundamental & clinical pharmacology
	Type of Study	Cross-Sectional Study & Retrospective study
	Number	42-550 (in adverse drug reactions (ADRs) spontaneously reported with methadone from 1996 to 2007)
	Other Medications Evaluated or Present	Amisulpride, Mianserine, Alimemazine, Cyamemazine, Fluoxetine
	Other Drugs of Abuse Evaluated	Codeine, Tobacco, Heroin, Amphetamine, Opiates, Alcohol
	Other Medical Conditions Evaluated	Depression, Insomnia, Anxiety Psychosis or personality disorders Hepatitis C HIV Cardiac arrhythmia Arterial Hypertension
	Major Findings	4 QTc prolongation in Cross Sectional Study 5 QTc prolongations (3TdP) and seven sudden cardiac deaths not correlated with Methadone overdose in retrospective study.
	Notes, Including Limitations	Small study group in Cross Sectional Study
<p>Methadone maintenance, QTc and torsade de pointes: who needs an electrocardiogram and what is the prevalence of QTc prolongation?</p> <p><i>Mayet S, Gossop M, Lintzeris N, Markides V, Strang J.</i></p>	Journal	Drug and alcohol review
	Type of Study	Cross-Sectional study
	Number	155
	Other Medications Evaluated or Present	Citalopram, Zopiclone, Salbutamol, Quetiapine, Chlorpromazine, Temazepam, Dexamphetamine, Olanzapine
	Other Drugs of Abuse Evaluated	Cocaine, Tobacco, Heroin, Benzodiazepine, Alcohol
	Other Medical Conditions Evaluated	Hepatitis C
	Major Findings	57.4% ($n = 89$) fulfilled MHRA criteria for ECG monitoring, QTc prolongation prevalence was 18.1% with NO 'clinically significant' QTc prolongation >500 ms or torsade de pointes known to be present
	Notes, Including Limitations

Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. <i>Anchersen K, Clausen T, Gossop M, Hansteen V, Waal H.</i>	Journal	Addiction (Abingdon, England)
	Type of Study	Mortality assessment study
	Number	173 patients on methadone
	Other Medications Evaluated or Present	N/A
	Other Drugs of Abuse Evaluated	N/A
	Other Medical Conditions Evaluated	N/A
	Major Findings	4.6% (n = 8) had a QTc above 500 milliseconds; 15% (n = 26) had a QTc interval above 470 milliseconds; and 28.9% (n = 50) had a QTc above 450 milliseconds. A positive dose-dependent association was identified between QTc length and dose of methadone, and all patients with a QTc above 500 milliseconds were taking methadone doses of 120 mg or more. OMT patient mortality, where QTc prolongation could not be excluded as the cause of death, was 0.06/100 patient-years. Only one death among 3850 OMT initiations occurred within the first month of treatment.
Heterogeneous impact of methadone on the QTc interval: what are the practical implications? <i>Krantz MJ</i>	Notes, Including Limitations	
	Journal	Journal of addictive diseases
	Type of Study	Prospective Cohort Study
	Number	151
	Other Medications Evaluated or Present	N/A
	Other Drugs of Abuse Evaluated	N/A
	Other Medical Conditions Evaluated	N/A
Corrected-QT intervals as related to methadone dose and serum level in methadone maintenance treatment (MMT) patients: a cross-sectional study. <i>Peles E, Bodner G, Kreek MJ, Rados V, Adelson M.</i>	Major Findings	The proportion exceeding 450 msec increased from 7% at baseline to 19% at 6 months; those exceeding 500 msec increased from 0% to 2%. Although 18% of subjects had an increase in QTc of 30 msec, only 3% had an increase exceeding 60 msec.
	Notes, Including Limitations	Critical QTc prolongation (exceeding 500 msec or increases exceeding 60 msec) occurred infrequently. This highlights the heterogeneity of QTc interval changes and measurement variability but also implies that electrocardiography screening among opioid dependent patients would only occasionally require methadone discontinuation.
	Journal	Addiction (Abingdon, England)
	Type of Study	Cross-sectional study
	Number	138
	Other Medications Evaluated or Present	Propanolol, Aspirin, Mirtazapime sodium, Valproate Acetylsalicylic Acid Simvastatin, Ramipril, Isosorbide Mononitrate Clonazepam, Fluoxetine Thyroxine sodium, Salbutamol, Enoxaparin, Haloperidol, Biperiden
	Other Drugs of Abuse Evaluated	Benzodiazepine, Opiate Cannabis Cocaine Amphetamine
QTc interval prolongation in patients on long-term methadone maintenance therapy. <i>Maremmanni J, Pacini M, Cesaroni C, Lovrecic M, Perugi G, Tagliamonte A.</i>	Other Medical Conditions Evaluated	HIV, HVB, HVC
	Major Findings	Mean methadone dose was 170.9 +/- 50.3 mg/day and mean serum methadone level was 708.2 +/- 363.1 ng/ml. Methadone dose and serum levels did not correlate with QTc. Three patients had QTc intervals above 500 ms (prolonged). After 2 +/- 0.4 years of follow-up, two patients died; they were two of three patients with very prolonged QTc. Causes of death were not attributed to cardiac origin.
	Notes, Including Limitations	Methadone maintenance is generally safe; however, the possible toxicity of high dose (> 120 mg/day) should be monitored for QTc
	Journal	European addiction research
	Type of Study	Prospective study
	Number	83
	Other Medications Evaluated or Present	N/A
	Other Drugs of Abuse Evaluated	N/A
	Other Medical Conditions Evaluated	N/A
	Major Findings	Eighty-three percent of the subjects had a more prolonged QT df (QT df is the difference between QTc and standardized values and it corresponds to the gap between an individual's QT and the expected for healthy subjects) than the reference values for persons of the same sex and age. Only 2 patients displayed a QTc interval of >500 ms. No correlation emerged between QTc values and methadone dosages.
	Notes, Including Limitations

<p>Levo-alpha-acetylmethadol (LAAM) induced QTc-prolongation - results from a controlled clinical trial.</p> <p><u>Wieneke H, Conrads H, Wolstein J, Breuckmann E, Gastpar M, Erbel R, Scherbaum N.</u></p>	Journal	European Journal of Medical Research
	Type of Study	Experimental study
	Number	22 in methadone group
	Other Medications Evaluated or Present	An patient with abnormal QTc interval received tricyclic antidepressant.
	Other Drugs of Abuse Evaluated	Urine drug screening revealed continuous use of cocaine during the study in one patient with abnormal QTc intervals.
	Other Medical Conditions Evaluated	Subjects with known cardiac disease were excluded
	Major Findings	No significant change in QTc interval in methadone group ($0.406 \text{ s} \pm 0.029 \text{ s}$ at run-in versus $0.405 \text{ s} \pm 0.025 \text{ s}$ at 24 weeks)
	Notes, Including Limitations	84 subjects were initially enrolled in the study and 53 complete ECG data sets could be obtained. It reflects the difficulties in conducting clinical studies in this patient group and has also been reported from other studies
<p>QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial.</p> <p><u>Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MC.</u></p>	Journal	Archives of internal medicine
	Type of Study	Experimental study (Randomized double-blind clinical trial)
	Number	Analyses were limited to the 154 patients and among them 55 in methadone group started the study and 32 finished it
	Other Medications Evaluated or Present	One participant used Erythromycin (potentially prolonging the QT)
	Other Drugs of Abuse Evaluated	N/A
	Other Medical Conditions Evaluated	N/A
	Major Findings	Using the categorical definition for QTc prolongation of more than 470 milliseconds for males and more than 490 milliseconds for females prolongation occurred among 23% of the methadone group ($P < .001$). An absolute QTc value of more than 500 ms occurred among 6 of 52 individuals in the methadone group ($P < .001$) at some point during the trial By stringent standard of an increase in QTc from baseline of more than 60 milliseconds at any time during the study 12% of subjects treated with methadone (OR, 8.4; 95% CI, 1.9-36.4) showed this increase
	Notes, Including Limitations	Female sex has been associated with considerably higher risks for QT prolongation and TdP but in the present study there was no significant difference between men and women with respect to prolongation more than 60 milliseconds from baseline ($P=.68$).
<p>Effects of methadone on QT-interval dispersion.</p> <p><u>Krantz MJ, Lowery CM, Martell BA, Gourevitch MN, Arnsten JH.</u></p>	Journal	Pharmacotherapy
	Type of Study	Prospective cohort study
	Number	118 patients who were newly admitted to the facility
	Other Medications Evaluated or Present	Isoniazid Antiretroviral agents Antidepressants Diuretics Calcium channel blockers Beta blockers Phenytoin
	Other Drugs of Abuse Evaluated	Cocain, Alcohol (> 10 drinks a week)
	Other Medical Conditions Evaluated	Hepatitis C, HIV Cardiovascular disease Hypokalemia
	Major Findings	Methadone modestly but statistically significantly increased both QTc interval and QT dispersion.
	Notes, Including Limitations	Baseline clinical variables tested for association with QT dispersion were age, sex, taking drugs that affect cardiac repolarization or methadone metabolism, self-reported cardiovascular disease, use of cocaine at baseline, and infection with human immunodeficiency virus or hepatitis C and the only one associated with the magnitude of QT dispersion at baseline was self-reported cardiovascular disease (42.1 vs 31.7 msec, $p<0.01$). The same clinical variables were then tested for association with the magnitude of change in QT dispersion over 6 months. Only concurrent antidepressant therapy was associated with a greater increase in QT dispersion (20 vs 8.5 msec, $p=0.04$).

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Impact of methadone treatment on cardiac repolarization and conduction in opioid users. Martell BA , Arnsten JH , Krantz MJ , Gourevitch MN	Journal	American Journal of Cardiology
	Type of Study	Prospective cohort study
	Number	At baseline 233 participants, ECG obtained from 149 after 6 months study period and 97 patients had all three ECG's done after 12 months; 108 participants had ECG at baseline and 12 months (without ECG recording after 6 months period)
	Other Medications Evaluated or Present	Isoniazid, Antiretroviral agents, Antidepressants, Diuretics, Calcium channel blockers, Beta blockers, Phenytoin
	Other Drugs of Abuse Evaluated	Cocain, Alcohol (>10 drinks a week), Benzodiazepine
	Other Medical Conditions Evaluated	Hepatitis C, HIV Cardiovascular disease, Hypokalemia
	Major Findings	The QTc interval increased significantly from baseline at both time intervals but the mean difference in QTc interval from 6 to 12 months was not significant ($p = 0.4$). At baseline, 5 subjects (3%) had prolonged QTc intervals, defined as >450 ms for men ($n = 3$) and >470 ms for women ($n = 2$). At 6-month follow up, 18 subjects (13% of men and 11% of women) had prolonged QTc intervals, and 2 patients had QTc intervals of >500 ms. At 12 months, 14 subjects (20% of men and 2% of women) had prolonged QTc intervals, and 2 patients had QTc intervals of >500 ms.
	Notes, Including Limitations	At the 12-month follow-up visit, a subset of 44 patients had same-day serum methadone concentrations measured at trough (immediately before daily dose) and peak (2 hours after daily dose) time intervals. In univariate analysis, only the methadone dose was significantly associated with the magnitude of the QTc increase from baseline to 6 months ($r = 0.18$, $p = 0.03$). In multivariate analysis, controlling for all factors associated with the baseline QTc interval and use of heroin, cocaine, and/or benzodiazepines, factors that were associated with greater QTc prolongation from baseline to 6 months, included male gender, HIV infection, and methadone dose. In multivariate analysis after 12 months, methadone dose remained marginally associated with the magnitude of the QTc increase ($p = 0.08$). The QTc interval change from baseline to 12 months was significantly correlated with the methadone trough ($r = 0.37$, $p = 0.008$) and peak levels ($r = 0.32$, $p = 0.03$).

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