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## Opioid Treatment and “Long-QT Syndrome (LQTS)”: a Critical Review of the Literature

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### Summary

The present review aims at perusing the available literature about QT-related cardiac safety during methadone treatment. On the whole, case reports, either single or multiple, do not seem a reasonable bases to draw conclusions about the weight of any putative risk factor for QT prolongation. On the other hand, systematic studies allow making some statements about the extension and weight of QT prolongation during methadone maintenance treatment for heroin addiction. No major concern about cardiac safety of methadone itself in the average addict seems to stand. Conditions at higher risk of multiple and polydrug treatments deserve some greater surveillance. No rationale for a dose-ceiling stands in a risk/benefit perspective.

*Key Words:* Opioid Treatment; Long-QT Syndrome; Review

### 1. Long QT Syndrome (LQTS): definition and clinical parameters

A survey of the critical literature shows that the acronym QT is currently interpreted as QT<sub>c</sub> (i.e. QT corrected for heart rate) [6, 25, 63].

The long QT syndrome (LQTS) is characterized by a disposition towards lengthening of the QT interval for no known reason, implying an increased risk of ventricular arrhythmias including torsades de pointes and ventricular fibrillation (with the former sometimes evolving into the latter) [49, 52, 53, 68].

A diagnosis of LQTS is based on the finding of a long QT indicating the likelihood of a future onset of clinical manifestations associated with the syndrome. The values recorded went from 0.41 sec to 0.65 sec, a range making them comparable with those obtained from many subjects with a normal QT interval [26]. In particular, 10% of subjects display an initial QT value no higher than 0.44 sec, and 30% between 0.45 and 0.47 sec, with a mean of 0.49 sec. Threshold values for a casually observed ‘suspect’ prolongation of QT vary: some authors suggest 0.48 sec for women and 0.47 sec for men [69], whereas

others propose 0.46 and 0.45 sec, respectively [53]. A diagnosis of LQTS may at times be formulated in the 0.41-0.47 sec range for males and 0.43-0.48 sec for females; below this threshold an LQTS diagnosis becomes highly unlikely. The Italian Medicines Agency (AIFA) indicates values below 0.43 and 0.45 sec as normal in adult men and women, respectively; 0.45 and 0.47 sec constitute borderline values and 0.45 and 0.47 sec indicating the presence of LQTS [59, 61, 74].

Since a ‘tail’ of QT value distribution in arrhythmic patients overlaps QT, lengthening can be applied as a risk factor allowing discrimination. Prolongation exceeding 30 msec is at risk, whereas an increase going beyond 60 msec shows that a critical threshold has been passed [31, 63]. In the course of ventricular arrhythmias, or shortly before their onset, the QT interval tends to increase progressively, reaching values exceeding 0.5 sec [7]. As no clear-cut association can be established between long QT and LQTS for values below 0.5 sec, this value is considered the clinically specific threshold (whether observed in the course of arrhythmias or immediately prior to their onset). Therefore, values ‘at risk of prolongation’ are highly variable, though it can be stated that values

exceeding 500 msec will only be reached if baseline levels were initially close to this threshold.

In conclusion, an ECG finding of a prolonged QT interval bridges the gap, with a certain margin of error, between the genetic, or acquired 'patophysiological' basis of LQTS and its clinical expression. Thus, subjects with a QT interval exceeding 0.5 sec, and a recent lengthening of QT interval of 40 msec or more, corresponding to a final QT value of over 0.41 sec, should be considered at risk of arrhythmia [59]. An additional parameter to be considered is a QT dispersion of more than 100 msec [40]. In a 12-lead ECG recording, dispersion of the QT interval (QTd) is the difference between the longest and the shortest QT interval, and is used to assess the difference in ventricular repolarization.

LQTS features a broad array of genetic, molecular and patophysiological structures [66, 67]: when corresponding to an alteration of phase III K<sup>+</sup> currents (with LQT1, LQT2, LQT5, LQT6 covering 90% of all cases), torsades de pointes (TdP), at times evolving into ventricular fibrillation, may be observed. The LQT3 form, linked to the gene coding for the voltage-gated Na<sup>+</sup> channel (SCN5A), is mainly expressed as ventricular fibrillation without TdP (10% of cases) [8-10, 16, 35, 68].

Cases of LQTS in a pure form are extremely rare (only 1 in 5000), although studies are currently under way to ascertain the associated genes. A clear majority of cases feature combined risk factors, at least partly concurrent with the manifestation of arrhythmias (acquired or 'mixed' forms).

The physiopathology of acquired forms of LQTS is comparable to that observed in forms of genetic origin, the only substantial difference being that it is induced by external factors. As a result, the ECG parameters featured are similar. A predisposition to acquired LQTS is not determined merely by genetic factors, but rather by a series of congenital and acquired factors that still needs to be fully clarified. Accordingly, additional unknown factors may be implicated in eliciting a varying response to a drug capable of prolonging the QT interval. As to the drug-induced risk threshold for LQTS, in cases of torsades de pointes appearing after the initiation of treatment for non-cardiac issues, as many as 92% had QT values exceeding 0.5 sec [7]. The risk threshold may therefore be fixed at 0.5 sec.

In the group of LQTS associated with specific drugs, additional risk factors may be involved, including: female gender (70%) [18, 45], hypokalaemia (39%), pre-existing structural cardiac disorders (41%), multiple drug treatments with drugs capable of prolonging the QT interval (28%) [14, 62, 70]. An association between drug-induced LQTS and a genetic substrate for LQTS is found in 18% of cases, so demonstrating that there is no precise clinical separation between genetic and acquired forms. The genetic forms tend to be clinically manifested in the presence of acquired factors [51]. The mechanism through which drugs induce LQTS is linked

to an interference with the channel-proteins that regulate cardiac repolarization. In particular, methadone interferes with the subunit encoding for the HERG/LQTS2 gene. The latter interference is not linked to the opioid activity being expressed; in fact, several opiate drugs, such as methadone, phentanyl and LAAM produce a markedly higher degree of interference (two orders of magnitude) compared to morphine and codeine [34].

## 2. LQTS and methadone treatment: a review of the literature

The definition of drug-related risks implies a systematic monitoring of patients. For drugs already on the market, a risk assessment should be carried out, taking into account the frequency of adverse cardiac events or an 'excessive' cardiac mortality rate among users of the drug since its introduction. In this connection, a positive long-term general safety profile has been demonstrated for methadone [12, 29, 32, 54].

In the absence of consistent retrospective evidence, recent warnings may reveal the expression of a selective focus on a single putative risk factor, and thus be biased by previous warnings issued on the same subject (e.g. the most likely rationale underlying the publishing of case reports seems to be the previous publication of similar case reports). The emergence of a risk of LQTS in subjects in long-term treatment with a specific drug who have shown no signs of adverse cardiac events suggests that increasing attention should be focused on new potential risk factors affecting recent consumers of that drug. With regard to methadone-maintained subjects, these factors may be associated with an increased use of anti-retroviral or anti-infective drugs, due to favourable therapeutic conditions induced by methadone treatment, or with an increased use of psychiatric drugs due to the furthering of knowledge of the association between opioid dependence and mental illness [28, 60, 73].

Substance abuse, in particular of alcohol and cocaine, may constitute an additional erratic, but still significant, factor [41, 55].

### 2.1 Case reports and case series

The practice of case reporting may, indeed, provide useful indications for research. On the other hand, a methodological distinction needs to be made between primary and secondary case reports. Secondary case reports are those with a rationale based on previously published primary reports that may have stimulated a selective focus on a given aspect or factor. In other words, secondary case reports feature no degree of spontaneity or originality. When secondary case-reports continue to be submitted to journals in spite of the publication of studies performed on larger samples, they become virtually superfluous, because the scientific value of a large body of secondary reports is no higher – statistically speaking

– than that of the original ‘primary’ report.

Naturally, when many reports all focused on a single drug build up over a relatively short period, that seems to suggest that a greater risk is attached to the drug concerned, but only as long as the presence of other risk factors in the sample can be ruled out. The publication of a series of reports on any given drug (e.g. methadone) known to be associated with other risk factors may well be due to a particular show of interest in that specific drug, so providing only a partial view of the actual epidemiological weight of the drug. When dealing with a syndrome such as LQTS, whose clinical expression is probably based on a range of precipitating factors, an observation focusing on a single factor in a selected population may well prove to be biased.

On the whole, case reports published on methadone and LQTS [27, 39, 50, 64, 71] essentially indicate that a combination of a series of arrhythmogenic factors may lead to the onset of torsades de pointes in subjects who have no pre-existing (genetic) predisposition to LQTS. Findings like these should not be viewed merely as ‘examples’ of methadone-related arrhythmias, but rather as cases strengthening the view that methadone administration may lead to the onset of arrhythmias.

Prospective evidence basically points to a normalization of the QT interval after an arrhythmic episode, once the methadone dose has been reduced or discontinued. This finding is not, however, sufficiently specific, in view of the fact that, theoretically, the discontinuation or reduction of other concomitant treatments may also lead to QT normalization and a fall in the risk of arrhythmias. As an example, out of a total of 4 cases studied by Gil [27], the QT interval returned to normal (0.38 sec) in only one patient after methadone discontinuation, although the methadone-free mean recorded was 0.47 sec. In ten cases described by Piguet [58], QT was shortened following a reduction of both methadone and other concomitant drugs. Moreover, in the course of treatment of arrhythmias, potential risk factors (e.g. electrolyte imbalance) are obviously monitored. Sticherling described five cases, all of them comprising additional risk factors for prolongation of QT interval that, once corrected, led to the normalization of QT values [65].

Not all case reports refer to a therapeutic setting or to the administration of prescribed dosages. A report published by De Bels [13] provides details of two cases of overdose from non-therapeutic administration of street methadone within a context of polydrug abuse, while one of the cases described by Walker refers to a rapid dose-escalation from 330 to 880 mg/die over the days immediately prior to an arrhythmic episode due to insufficient pain coverage [71]. The patient described in a report by Decerf [15] died three days after the abrupt reintroduction of methadone at a previously administered dose of 130 mg/die subsequent to a twelve-day withdrawal period.

In a study investigating 17 individuals, Krantz [38] indicates methadone as the only common predictive factor,

in spite of the presence of other, more variable risk factors. Moreover, only subjects with a QT interval exceeding 0.5 sec were included in the study. The finding of a dose-QT correlation is therefore not a naturalistic observation, as it only includes subjects showing a pathological prolongation of QT interval and signs of LQTS.

A correlation between methadone dose and QT detected in patients who had been referred for treatment of arrhythmias or arrhythmic syncope is only significant when related to patients affected by arrhythmia, not to methadone-treated subjects in general.

In a review of 40 cases, Justo and co-workers stressed that all patients (affected by clinically diagnosed LQTS) featuring a pathological lengthening of the QT interval (mean 598 msec), were taking high doses of methadone and, in approximately 25% of these cases, were marked out by other single or combined risk factors for QT prolongation. In particular, about 1 patient in every 4 was suffering from a cardiac disease, with an even higher rate of liver or kidney failure. 40% of subjects were HIV+ and 35% presented hypokalaemia [33]. The limitations observed were similar to those revealed for single case reports or case-series.

### 2.2 Arrhythmic mortality and long QT in methadone-treated subjects

Data provided by the FDA (Food and Drug Administration) confirm that 0.78% (59 cases) of adverse events reported during methadone treatment from 1969 to 2002 took the form of TdP, with 3 out of 4 cases displaying additional risk factors for LQTS [56]. A retrospective study of 2382 patients reported an estimated death rate of 0.06 per 100 patient-years [2].

Fanoie et al. carried out a study to investigate the correlation between therapeutic status and a history of syncope in a group of 450 heroin addicts, demonstrating a correlation between doses exceeding 50 mg and probable onset of syncope. No clear-cut results were, however, obtained due to the difficulties encountered in defining syncopal episodes [22].

In a group monitored by Peles, 3 patients displaying a prolongation of the QT interval of over 500 msec had all died from other causes at two-year follow-up [57].

### 2.3 Long QT in methadone-treated subjects: prospective, cross-sectional and retrospective studies

Overall, most of the studies present in the literature report mean QT values below the 450 msec threshold [4, 11, 30, 46, 47].

In a prospective study undertaken by Wedam to compare equally potent doses of buprenorphine, methadone and LAAM, 21% of subjects displayed QT values exceeding 470 msec (males) or 490 msec (females) throughout a 17-month treatment with methadone, yielding a result intermediate between findings obtained with LAAM

(28%) and buprenorphine (0%). Approximately 11% of methadone- and LAAM-treated subjects displayed QT values of more than 0.5 sec in at least one monthly ECG recording performed throughout the study period (vs. 0% on buprenorphine). Methadone-related prolongation of the QT interval occurs gradually over the first 8 weeks, contrary to observations made with other drugs; this could be due to a diverse rapidity of dose-escalation, or to pharmacological differences between the compounds [72].

In a study published by Peles (in a predominantly male sample), approximately 16% of subjects presenting a prolonged QT exceeding 450 msec in the course of methadone treatment lasting from 3 months to several years. Contrary to previous studies, prolongation of the QT interval to over 0.5 sec was only observed in 3 (2%) of these subjects [57].

Cruciani and co-workers observed a mean value slightly below the threshold for risk (428 msec), even if 33% of subjects studied presented a prolongation of QT interval. In any case, no high-risk values (>0.5 sec) were detected [11].

Maremmani et al. reported QT values for subjects on methadone treatment somewhat higher than expected as to age and sex, although exceeding 0.5 sec in just 2 cases; none of these subjects had any previous history of cardiovascular events [46]. Similarly, Fonseca and colleagues found a moderate prevalence (9.2%) of high QT values (> 440), but rarely (1.8%) higher than 500 msec [23].

A cross-sectional controlled study performed on a small group of methadone-treated subjects found no difference between methadone and buprenorphine, reporting a tendency towards higher values within the safety range (405 msec) in subjects taking methadone doses of over 60 mg/die [4].

In a study undertaken by Ehret and co-workers, 16.2% of patients displayed a QT above 500 msec versus 0% in the control group; 3.6% (6) of subjects showed TdP, although the weight of methadone as a causal factor for the onset of TdP in this subgroup was calculated to be approximately 30%. It should be noted that all the patients studied were heroin addicts admitted to hospital for various reasons. The sample displaying TdP were all polydrug users (median 9 vs. 4 in the control group) [19].

#### 2.4 *Prospective studies on QT prolongation in subjects on methadone treatment*

With specific reference to prolongation of the QT interval in the course of methadone treatment, Krantz [37] reported an average increase in QT of approx. 14 msec at 6 months; Wedam and co-workers [72] 17 msec in at least one recording performed during the stabilization period (subsequent to the first month); Martell reported a 12 msec prolongation at 6 months and 11 msec at 12 months [47]. Chronic pain patients switching from mor-

phine to methadone displayed a very limited (5 msec), but still significant increase in the QT interval [24]. Fanoë calculated an increase of 0.14 msec/mg oral methadone: considering a mean effective dose (80-120 mg/die), this would correspond to approximately 14 msec [22].

A prolongation of the QT interval beyond 60 msec was observed in 12% of cases (intermediate between the 21% reported for LAAM and 2% buprenorphine) in the study carried out by Wedam and colleagues [72].

A mean 7-8% increase should be expected over the first two months of treatment. The final value reached is invariably below the 450/470 msec threshold in substance-free subjects [30].

It would seem that the finding of a prolongation of the QT interval is a relatively frequent occurrence [30, 72]; when compared to values obtained in controls (detox, pre-treatment), any methadone-related lengthening is invariably quite limited [22, 24, 30, 47, 72]. In studies performed on samples of asymptomatic subjects, the finding of risk values is a relatively rare event, and is most frequently observed, as might be expected, in selected hospitalized samples.

Dispersion of the QT interval never exceeded 0.1 msec, although an increase was observed in subjects on concomitant treatment with methadone and antidepressants [37].

Athanasos and co-workers [4] specifically report a higher dose-dependent rate of U waves in ECG recordings from subjects on methadone rather than buprenorphine treatment. This finding confirms the frequent observation (32%) of U waves in methadone-maintained subjects [44]. The waves observed are 'physiological' U waves, merging with T waves and thus included in measurement of the QT interval [1].

The final interpretation of the findings obtained in several of the above studies has a rather limited scope, however. At variance with other studies, the paper that reported the highest percentage of cases in which QT lengthening went beyond 0.5 sec [72], while it provided no details of drug abuse, ruled out the involvement of prescription drug-related pharmacological factors; its inclusion criteria was simply that of a prolongation of the QT interval recorded in at least one monthly ECG: a prolongation of that kind could have been no more than a chance finding.

The results obtained by Fanoë [22], in a study comprising subjects with a history of syncope treated with low doses of methadone — subjects who had not necessarily been stabilized — cannot however be adequately interpreted to allow for a risk-benefit assessment. Maremmani and co-workers attempted to investigate a sample of stabilized heroin addicts free from all other substances of abuse, who then underwent methadone treatment at a mean dose of approx. 90 mg/die. In their sample, which was selected for its suitability for a risk-benefit assessment, a 2.4% incidence rate was reported for prolonged QT, with no relevant clinical associations [46].

Injectable methadone can likewise induce prolongation of the QT interval. The study carried out by Mayet and coll. [48] had the major limitation that it did not rule out the possible concurrent use of cocaine, which was documented in 53% of subjects on enrolment. Episodes of QT lengthening were observed quite frequently, although no constant values were obtained and prolongation could not be associated with any specific ‘acute’ action. Kornick and coll. found a dose-dependent average prolongation of 41 msec (measured before and after i.v. methadone) compared to 9 msec with i.v. morphine, which, incidentally, demonstrated the weaker effect on QT produced by the solvent chlorbutanol. The latter study was a retrospective observation of inpatients suffering from neoplastic diseases who had been taking methadone for pain control purposes [36].

### 2.5 Quantitative correlations

Generally speaking, no constant dose-effect correlation has been reported. It is, however, true that Peles et al. observed a more marked prolongation of the QT interval at methadone doses exceeded 120 mg, even if no dose-effect correlation could be confirmed [57].

A similar, small but significant correlation (2 msec mean difference) was revealed by Martell in subjects taking methadone doses over 110 mg/die [47]. Athanasos and co-workers reported a difference in QT prolongation with methadone doses below and above 60 mg/die, but invariably below risk values (381 msec vs 405 msec) [4]. Cruciani and colleagues found a correlation only in male subjects on methadone for less than one year [11], a finding not confirmed by Marenmani [46].

In the treatment of addiction, it is noteworthy that oral methadone doses correspond to blood methadone levels that may vary widely: by contrast, doses that exceed 200 mg correspond to a narrow range of blood levels, due to a faster hepatic metabolic rate [42]. When higher doses are administered to chronic pain patients, they may actually correspond to higher blood methadone levels, and rapid dose escalation can be resorted to in treating renewed pain. In the multiple case report published by Krantz, blood methadone levels were referred to as being “higher than expected”.

It can be concluded that the rationale underlying the administration of high doses of methadone in the treatment of drug abuse differs from that applied in the treatment of chronic pain. In the latter case the use of extremely high methadone doses probably leads directly to an effective increase in expected blood methadone levels.

Methadone is produced as a racemic mixture. The inactive isomeric S form displays a higher (3.5-fold) potency than the hERG current [43]. Special care should therefore be taken in managing the drugs which act as inhibitors of the S-methadone metabolism that is regulated by CYP2B6 (the substrate-inhibitors ifosfamide and cyclofosfamide, thiotepa, ticlopidin, efavirenz and

bupropion). Subjects displaying a slow metabolic clearance of S-methadone — those running a particularly high risk of LQTS — accounted for 6% of the sample studied by Eap and co-workers [17].

On the contrary, Fonseca and colleagues failed to detect any correlation between plasma concentration of isomers and QT values [23].

Turning now to the metabolic interactions with active R-methadone isomers, mainly CYP3A4 and 2D6 inhibitors, no additional methadone-related risks are actually expected when doses are titrated on a clinical basis, as blood methadone levels will be higher than expected, corresponding to lower oral doses.

An increased risk of LQTS may, however, be implicated when methadone administration is associated with drugs known to raise blood methadone levels and prolong the QT interval. The concomitant administration of drugs known to increase blood methadone levels may create a false impression of a drug-induced improvement of psychiatric symptoms, when this is actually produced by an increase in blood concentrations; in these cases, the QT interval may be prolonged to a greater extent than it is after the administration of a higher dose of methadone.

### 3. Buprenorphine and lengthening of the QT interval

Studies undertaken to investigate buprenorphine provide indications confirming the relative neutrality of the drug with regard to the risk of prolonging the QT interval. Two prospective studies failed to find any cases of long-term prolongation of the QT interval exceeding 450 msec (or 470 in females) [72]. Likewise, in a retrospective study of 200 cases, none of the QT values exceeded 450 msec [72].

Despite this, a few (2%) cases of pathological ‘lengthening’ beyond 60 msec may be observed, without ever reaching the threshold for risk values. [72]. As a general rule, subjects treated with buprenorphine alone are not susceptible to significant changes in QT values [5].

In a comparative cross-sectional study, buprenorphine was seen to be associated with QT values similar to those found during methadone treatment and in control groups [4], while a further study performed to compare methadone with LAAM showed that buprenorphine - neutral - gave results that differed from those of the other two treatments [72].

Two incidental findings have been described in which buprenorphine was administered as an alternative to methadone in subjects developing overt clinical LQTS [21, 37].

### 4. Recommendations

The evidence provided suggests the advisability of great caution in managing methadone-treated patients featuring multiple risk factors for ventricular arrhythmias.

As a general rule, in the course of methadone treatment a prolongation of the QT interval not exceeding threshold risk values can be expected. The extent and frequency of QT lengthening are considerably lower than those reported for LAAM [72], which was withdrawn from the European market because it raised the risk of arrhythmias [20]. The following recommendations may therefore be put forward for the task of defining and monitoring arrhythmias in methadone-treated patients:

a) patient and family history of LQTS (recurrent syncope of unknown origin, sudden death) should both be ascertained;

b) potential drug-associated risk factors for LQTS should be recorded;

c) ECGs whose aim is to identify cases of overt LQTS should only be resorted to before the start of treatment if and only if a given case includes known and/or suspected risk factors. If subjects of this kind are treated with methadone, an ECG should then be performed periodically to monitor developments, as an onset of LQTS could occur during treatment. The above procedure should also apply when there is a positive history, or with the use of cocaine or any other illicit substance capable of prolonging the QT interval;

d) avoid the association of methadone with drugs capable of prolonging the QT interval [3], unless strictly necessary, particularly in the case of double diagnosis and when prescribing drugs that inhibit the methadone metabolism. When a drug association is required, an ECG should be performed to monitor for variations in QT length;

e) on the basis of the risk parameters displayed (length, prolongation, dispersion) and also of the range of risks involved, the possibility of resorting to alternative treatments or lower doses should be taken into account in stabilized patients undergoing long-term treatment, or other concomitant treatments modified according to an established scientific hierarchy, bearing in mind that a discontinuation of methadone treatment may also affect compliance with other associated treatments (e.g. anti-infective or psychiatric drugs);

f) in LQTS cases that comprise critical episodes, establish an alternative treatment or assess the suitability of a pacemaker implant.

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