# Synthetic cannabinoids and potential cardiac arrhythmia risk: an important message for drug users

*Ther Adv Drug Saf*

2020, Vol. 11: 1–4

DOI: 10.1177/2042098620913416



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$\Delta^9$-Tetrahydrocannabinol, the psychoactive ingredient in cannabis, and synthetic cannabinoid receptor agonists (SCRAs) activate the CB1 receptor to produce their profound behavioural effects and are widely used as recreational drugs. There is growing evidence that SCRAs, commonly known by the street name Spice or K2 (though there are many others, see: http://www.emcdda.europa.eu/publications/drug-profiles/synthetic-cannabinoids) can produce detrimental cardiovascular effects.[1] Commonly observed cardiotoxic effects of SCRAs include tachycardia, chest pain and hypertension.[1] However, bradycardia and hypotension have also been reported in K2-induced toxicity.[2] Here, we consider evidence of cardiac repolarization abnormalities following SCRA use, an issue that may be of particular significance to individuals also receiving psychiatric or opiate substitution prescription medications, but that is also of potential significance to patients receiving other prescription or recreational drugs.

One of the issues in evaluating cardiotoxicity of SCRAs is that, due to a setting of recreational rather than clinical drug use, the composition of street drugs can be variable and different chemical structures may interact in unpredictable ways.[1] Street preparations of SCRAs may contain varying (and unknown to the user) combinations of different SCRA compounds and, commonly, the dose taken is unknown. Most SCRA users are polydrug users, commonly using natural cannabis as well as SCRAs, with a significant minority also using stimulants,[3] which may complicate attribution of physical harms. However, there is a reported 30-fold odds (a per event risk of 0.0006017) of requiring emergency medical treatment following SCRA use over those who use cannabis alone (a per event risk of 0.0000201).[4] There is growing evidence for a risk of clinically significant prolongation of the rate corrected QT ($QT_c$) interval of the electrocardiogram (ECG) with SCRA use.[5–8] The principal arrhythmia associated with delayed ventricular repolarization, and hence with $QT_c$ interval prolongation, is torsades de pointes (TdP). This is linked to cellular genesis of early-after depolarizations and increased dispersion of repolarization,[9,10] and can degenerate into fatal ventricular fibrillation. Thus, $QT_c$ prolongation by both clinical and recreational drugs is a matter of some significance.

In 2014, Ibrahim and colleagues reported a case of cardiac arrest in a middle-aged male with concurrent coronary artery disease, within an hour of consumption of the SCRA product K2. He was successfully resuscitated, and his ECG on hospital admission showed a prolonged (though unspecified) $QT_c$ interval.[5] The patient did not show electrolyte abnormalities and a routine drug screen on admission was negative. The temporal relationship between K2 exposure and cardiac arrest and evidence of myocardial necrosis without acute coronary occlusion led the authors to consider K2 as a causative agent.[5] In 2016, Von Der Haar and colleagues reported the case of a 29-year-old male with a history of depression, who was admitted to an emergency psychiatric unit after smoking K2. He required sedation (with lorazepam and haloperidol) and, within 10 min of this, showed a $QT_c$ interval of 560 ms (compared with 412 ms from an ECG 8 months earlier). The patient had been prescribed sertraline and quetiapine for his psychiatric condition, which could also affect the $QT_c$ interval, but stated that he was noncompliant with these. Urine toxicology was conducted for barbiturates, benzodiazepines, cocaine, opiates, methadone, tetrahydrocannabinol, and phencyclidine and was found to be negative,[6] and electrolyte (magnesium and potassium) levels were normal. Whilst psychotropic medications are associated with $QT_c$ interval prolongation (e.g.[11]) the authors

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reasoned that this individual's noncompliance and earlier normal ECG argue against these as a primary cause of $QT_c$ prolongation, and that the prolongation of the $QT_c$ interval occurred too rapidly to be accounted for by intramuscularly (IM) administered haloperidol as a sedative.

Very recently, Yildiz and colleagues published an evaluation of ventricular repolarization parameters in 58 patients admitted to the emergency department following SCRA use.[7] Comparison of 12-lead ECG of these patients was made with that of 54 age- and sex-matched healthy controls, who had been referred to the cardiology outpatient clinic for evaluation and had not ingested a synthetic cannabinoid. The control subjects did not exhibit evidence of pathologies affecting ventricular repolarization parameters in noninvasive cardiac examinations.[7] ECG analysis focused on QT, (Bazett's corrected) $QT_c$ intervals and T-wave analysis.[7] Exclusion criteria for patient data included electrolyte disturbances, pre-existing heart disease and use of substances known to affect ECG parameters. QRS complex duration did not differ significantly, but $QT_c$ intervals were significantly longer in the SCRA group than in controls.[7] The authors also measured the interval between the peak and end of the T wave ($T_{p\text{-}e}$), as an index of transmural dispersion of repolarization, and found that this too was greater in the SCRA group than in controls. This significant difference persisted when $T_{p\text{-}e}$ was normalized to QT or $QT_c$ intervals.[7] Although none of the patients in this study had ventricular arrhythmias at the time of ECG measurement, the observation of increased $T_{p\text{-}e}$ has potential significance as a marker of arrhythmia risk in SCRA use: $T_{p\text{-}e}$ has been suggested to be the best predictor of TdP in acquired long QT syndrome.[12] Thus, these recent findings suggest that $QT_c$ prolongation with SCRA use is associated with increased heterogeneity of ventricular repolarization, which is likely to increase the propensity for ventricular arrhythmia. Consistent with this, a recent case has emerged of a 52-year-old female who had cardiac arrest shortly after first-time use of cigarettes laced with the SCRA product K2.[8] She was resuscitated out of hospital and then admitted. Her ECG showed a prolonged $QT_c$ interval of 534 ms and lateral T wave inversion. She experienced an episode of ventricular fibrillation in hospital that was seen to occur as TdP degenerating into ventricular fibrillation and was associated with a prolonged $QT_c$ of 634 ms. She had a reduced ventricular ejection fraction, which later improved. She received an implantable defibrillator due to two near-fatal arrests. Information on analytical screening, electrolyte levels and presence/absence of other potential $QT_c$ prolonging factors are unavailable for this case.

One limitation in evaluating the evidence linking SCRA use and $QT_c$ prolongation is the varying level of information between reports. For example, only Yildiz and colleagues stated which correction method was used to derive $QT_c$ interval values,[7] and there is little information on other factors that may predispose to QT prolongation in the study of Ahmed and colleagues.[8] Another limitation, highlighted by both Ibrahim and colleagues and Yildiz and colleagues,[5,7] is a reliance on self-reported drug history due to a lack of available drug screens for SCRA use. The development of (an) appropriate screen(s) is made difficult both due to the variable composition of SCRA products and the continuous emergence of novel SCRA entities.[5] Further patient studies, particularly systematic studies of multiple subjects who have taken SCRAs are therefore needed to explore further the effects of SCRAs on ventricular repolarization and arrhythmia risk.

Virtually all drugs that produce acquired long QT syndrome and TdP arrhythmia produce pharmacological inhibition of cardiac 'hERG' potassium channels.[10] The SCRA JWH-030 has been reported to inhibit hERG channel current ($I_{hERG}$), but with relatively low affinity ($IC_{50}$ of 88 μM).[13] The compound abbreviated rather than lengthened rabbit Purkinje fibre action potentials in the same study, however, suggesting that other effects outweighed hERG channel inhibition. Interestingly, JWH-030 prolonged the QT interval in ECG measurements from rats in the same study.[13] Rats do not rely on hERG for ventricular repolarization, so this observation raises the possibility that this SCRA may delay repolarization through a non-hERG mediated mechanism. However, other SCRAs, including JWH-018 and JWH-073, are more prevalent in recreational SCRA preparations,[14] and the effects of these compounds on hERG remain to be established.

Drug-induced TdP is usually a multiple-hit phenomenon, with known risk factors including metabolic disturbances and the presence of more

than one $QT_c$-prolonging drug.[15] The fact that many SCRA users may use additional prescription or recreational drugs is therefore a cause for concern. Patients taking psychotropic medications associated with $QT_c$ interval changes (a property often associated with antidepressants, mood stabilisers and antipsychotics) who are suspected of using SCRAs should be warned about potential additive or synergic effects in terms of cardiac risk. Similarly, patients taking methadone as substitution treatment for opioid dependence should be cautioned against taking SCRAs, as methadone itself is known to be linked to $QT_c$ prolongation and TdP,[16] and concurrent consumption of SCRAs may therefore be a dangerous but avoidable risk. Patients suspected of using SCRAs should undergo 12-lead ECG testing, have electrolyte levels tested and have a full history taken of prescription and recreational drugs. Opiate users should also be subject to additional ECG monitoring to ensure safe methadone prescribing, even at relatively modest doses, because of additive effects. Concurrent cocaine use is also a potential issue, given that cocaine itself has cardiotoxic effects involving hERG channels.[17] Finally, clinicians working in emergency settings should be mindful of QT prolongation in this population because it will affect safe management of behavioural disturbance. Due to their comparatively low propensity to prolong the $QT_c$ interval,[18] benzodiazepines may be preferable to major tranquillisers as an initial approach for patients who have taken SCRAs who require sedation. For cases where benzodiazepines do not suffice or are contraindicated, it should be noted that a recent meta-analysis found that intramuscular olanzapine was less likely to be associated with QT prolongation than haloperidol, making it the agent of choice for management of SCRA-related behavioural disturbance where IM medication is required.[19] It is worth noting that where IM olanzapine is given to patients already receiving benzodiazepines, and although a recent analysis has highlighted a lack of data causally linking this combination with severe adverse effects,[20] careful monitoring to avoid respiratory depression is nevertheless probably prudent. Further work is certainly warranted to evaluate the actions of key SCRAs on determinants of ventricular repolarization and to explore interactions between cardiac effects of these drugs and commonly used medications, including psychotropic drugs and methadone.

## Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

## Conflict of interest statement

The authors declare that there is no conflict of interest.

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