Further insights into inheritable arrhythmia syndromes: Focus on electrocardiograms
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Drugs and Brugada syndrome

Review of the literature, recommendations and an up-to-date website (www.brugadadrugs.org)

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ABSTRACT

BACKGROUND
Worldwide, the Brugada syndrome has been recognized as an important cause of sudden cardiac death at a relatively young age. Importantly, many drugs have been reported to induce the characteristic Brugada syndrome-linked ECG abnormalities and/or (fatal) ventricular tachyarrhythmias.

OBJECTIVE
The purpose of this study was to review the literature on the use of drugs in Brugada syndrome patients, to make recommendations based on the literature and expert opinion regarding drug safety, and to ensure worldwide online and up-to-date availability of this information to all physicians who treat Brugada syndrome patients.

METHODS
We performed an extensive review of the literature, formed an international expert panel to produce a consensus recommendation to each drug, and initiated a website (www.Brugadadrugs.org).

RESULTS
The literature search yielded 506 reports to be considered. Drugs were categorized to one of four categories: 1) drugs to be avoided (n=18), 2) drugs preferably avoided (n=23), 3) antiarrhythmic drugs (n=4) and 4) diagnostic drugs (n=4). Level of evidence for most associations was C (only consensus opinion of experts, case studies, or standard-of-care) as there are no randomized studies and few non-randomized studies in Brugada syndrome patients.

CONCLUSIONS
Many drugs have been associated with adverse events in Brugada syndrome patients. We have initiated a website (www.Brugadadrugs.org) to ensure worldwide availability on safe drug use in Brugada syndrome patients.
INTRODUCTION

Worldwide, the Brugada syndrome (BrS) is recognized as an important cause of sudden cardiac death occurring in individuals at a relatively young age. BrS is diagnosed in the presence of specific electrocardiographic abnormalities (known as the type-1 BrS-ECG) (figure 1) seen in combination with an absence of gross structural abnormalities and several other criteria.\(^1,2\) In addition, BrS often shows familial aggregation.

The presence of the type-1 BrS-ECG in particular has been linked to an increased risk for ventricular tachyarrhythmias, cardiac arrest and sudden death in BrS-patients.\(^3\) Importantly, many drugs have been reported to induce the type-1 BrS-ECG and/or (fatal) arrhythmias in BrS-patients (figure 2). Therefore, it is necessary to advice patients with BrS not to use these drugs, or to use them only in controlled conditions.

Although the most appropriate treatment in BrS is under discussion,\(^4,5\) avoidance of potential proarrhythmic drugs and fever (which is a well-known trigger of cardiac events in Brugada syndrome)\(^6,7\) are generally accepted to be an important part of (prophylactic) treatment. However, some patients may (only) be appropriately treated with an implantable cardioverter-defibrillator. Some drugs may have an antiarrhythmic effect and may thus be used favorably in the acute or chronic setting.\(^8-10\) As BrS has a rather low prevalence (estimated at 1 in 2,000, varying in different regions around the world),\(^1\) these and other critical characteristics of BrS may not be common knowledge for many physicians.\(^11\)

With the aim of aiding all physicians who treat patients with BrS, we discussed the interaction between drugs and BrS, performed an extensive review of the literature, formed an international expert panel to produce a consensus recommendation for each drug, and initiated a website (www.brugadadrugs.org) (figure 3) to ensure worldwide online and up-to-date information.

**Figure 1** The Brugada syndrome ECG

Conversion of a normal ECG to a type 1 Brugada syndrome ECG during ajmaline challenge. Note the coved-type ST segments (arrows) in the right precordial ECG leads at peak ajmaline (note that V3 is placed in the third intercostal space above V1 [V1ic3], and V5 is placed in the third intercostal space above V2 [V2ic3]).
availability of this knowledge base.

**METHODS**

**Literature review**

PubMed (Text: Brugada; MeSH Terms: Chemicals and Drugs Category; only reports in English were considered) and expert knowledge was employed to investigate drugs which have been associated with the type-1 BrS-ECG, with arrhythmias or with antiarrhythmic properties in BrS-patients. Although there is large variation in the extent to which different drugs have been associated with BrS, we aimed to investigate the first reported drug-BrS association for each drug, but favored larger, combined clinical-experimental or otherwise important studies (e.g., those which report arrhythmias). Thus, we refer to many, but not to all reports that describe a certain drug-BrS association. Furthermore, we sought drugs with cardiac ion channel blocking effects that, hypothetically, have the potential to have deleterious effects in BrS-patients but that have not yet been reported to have deleterious effects. Finally, for most drugs having a clinical association with BrS, we were able to retrieve confirmatory experimental studies showing the effects of the drug on the cardiac electrophysiology.

**Recommendations**

As there are no randomized clinical trials in BrS, the level of evidence (American College of Cardiology/American Heart Association/European Society of Cardiology [ACC/AHA/ESC] format) for most associations is C (only consensus opinion of experts, case studies, or standard-of-care) and for some associations B (non-randomized studies). To ascertain validity of recommendations given, we formed an international expert panel (the BrugadaDrugs.org Advisory Board) to summarize the clinical and experimental evidence and expert opinion. The classification of recommendation is expressed in a modified ACC/AHA/ESC format as follows:

- **Class I:** There is evidence and/or general agreement that a given treatment is potentially proarrhythmic (or potentially antiarrhythmic) in BrS-patients.
- **Class IIa:** There is conflicting evidence and/or divergence of opinion about the drug, but the

![Figure 2: Arrhythmia due to drugs](image-url)
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Introduction to BrugadaDrugs.org

BrugadaDrugs.org has been initiated by the University of Amsterdam Academic Medical Center, department of Cardiology, to aid physicians who treat patients with Brugada syndrome.

Worldwide, the Brugada syndrome has been recognized as an important cause of sudden cardiac death at a relatively young age. Brugada syndrome is diagnosed in the presence of specific electrocardiographic abnormalities (known as the type-1 Brugada syndrome ECG) combined with an absence of gross structural abnormalities and several other criteria. Further, Brugada syndrome often shows familial aggregation. The presence of this type-1 ECG in particular has been linked to an increased risk for ventricular tachyarrhythmias, cardiac arrest and sudden death in Brugada syndrome patients. Importantly, many drugs have been reported to induce the type-1 ECG and/or (fatal) arrhythmias in Brugada syndrome patients. Therefore, it is necessary to advice patients with Brugada syndrome not to use these drugs, or only in controlled conditions.

Figure 3  Screenshot of www.brugadadrugs.org

BrugadaDrugs.org has been initiated by the University of Amsterdam Academic Medical Center, department of Cardiology, to aid physicians who treat patients with Brugada syndrome.

Worldwide, the Brugada syndrome has been recognized as an important cause of sudden cardiac death at a relatively young age. Brugada syndrome is diagnosed in the presence of specific electrocardiographic abnormalities (known as the type-1 Brugada syndrome ECG) combined with an absence of gross structural abnormalities and several other criteria. Further, Brugada syndrome often shows familial aggregation. The presence of this type-1 ECG in particular has been linked to an increased risk for ventricular tachyarrhythmias, cardiac arrest and sudden death in Brugada syndrome patients. Importantly, many drugs have been reported to induce the type-1 ECG and/or (fatal) arrhythmias in Brugada syndrome patients. Therefore, it is necessary to advice patients with Brugada syndrome not to use these drugs, or only in controlled conditions.

Subsequently, we have listed the drugs into four groups:

- **Drugs to be avoided by BrS-patients**
- **Drugs preferably avoided by BrS-patients**
- **Potential antiarrhythmic drugs in BrS-patients**
- **Diagnostic drugs for BrS**

Within these groups we differentiated between different drug classes (e.g., antiarrhythmic drugs and psychotropic drugs).

weight of evidence/opinion is in favor of a potentially proarrhythmic (or potentially antiarrhythmic) effect in BrS-patients.

- **Class IIb**: There is conflicting evidence and/or divergence of opinion about the drug and the potential proarrhythmic (or potentially antiarrhythmic) effect in BrS-patients is less well established by evidence/opinion.
- **Class III**: There is very little evidence and/or agreement that a drug is potentially proarrhythmic (or potentially antiarrhythmic) in BrS-patients.
RESULTS

The PubMed search yielded 563 reports, including 506 written in English. The BrugadaDrugs.org Advisory Board selected about 15% of these reports as adding considerably to our knowledge and understanding of drug effects in BrS. The drugs and accompanying recommendation are listed in Tables 1 through 4.

DISCUSSION

In this study we reviewed the literature on the use of drugs in BrS-patients and made recommendations about their safety which was based on the literature and expert opinion. We also initiated a website (www.brugadadrugs.org) where these drugs and the recommendations can be accessed by all physicians who treat patients with BrS and by other individuals with possible interest (e.g., patients). On this website we provide more detailed information on drugs in BrS than reviewed in this article. Additionally, the website is frequently updated (drugs added or removed, recommendations changed) according to the latest evidence.

Patients with BrS should be advised not to take drugs from the ‘avoid’ and ‘preferably avoid’ lists or to use these drugs only after extensive consideration and/or in controlled conditions. We advise patients to give a list of these drugs to all their treating physicians (including their general practitioner, dentist, and pharmacist). In many BrS-patients, avoidance of these drugs (and treatment of fever)\textsuperscript{6,7} is probably appropriate and safe treatment. Some BrS-patients seem to perform well on quinidine.\textsuperscript{8-10} Recently a prospective registry has started investigating the use of empiric quinidine therapy for asymptomatic BrS-patients (ClinicalTrials.gov identifier NCT00789165).\textsuperscript{12} Further, the QUIDAM study (HydroQuinidined to Decrease Arrhythmic events in Brugada syndrome patients, ClinicalTrials.

| Table 1 | DRUGS TO BE AVOIDED |
|--------------------------------------------------|
| **Drug category** | **Drug (generic)** | **Recommendation** |
| Antiarrhythmic | Ajmaline\textsuperscript{26-29} | Class I |
| | Flecainide\textsuperscript{30-34} | Class I |
| | Pilsicainide\textsuperscript{35-38} | Class I |
| | Procainamide\textsuperscript{17,26,39,40} | Class I |
| | Propafenone\textsuperscript{41-45} | Class IIa |
| Psychotropic | Amitriptyline\textsuperscript{46-49} | Class IIa |
| | Clomipramine\textsuperscript{50,51} | Class IIa |
| | Desipramine\textsuperscript{52-55} | Class IIa |
| | Lithium\textsuperscript{52,56} | Class IIa |
| | Loxapine\textsuperscript{57} | Class IIa |
| | Nortriptyline\textsuperscript{55,58,59} | Class IIa |
| | Trifluoperazine\textsuperscript{57,60} | Class IIa |
| Anesthetic | Bupivacaine\textsuperscript{61-64} | Class IIa |
| | Propofol\textsuperscript{62,65-67} | Class IIb |
| Other | Acetylcholine\textsuperscript{17,68,69} | Class IIa |
| | Alcohol(toxicity)\textsuperscript{47,70,71} | Class IIb |
| | Cocaine\textsuperscript{72-75} | Class IIa |
| | Ergonovine\textsuperscript{68,76} | Class IIb |

Recommendation: Class I: convincing evidence/opinion; Class IIa: evidence/opinion less clear; Class IIb: conflicting evidence/opinion.
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gov identifier NCT00927732), a French national double blinded randomized study, is currently performed on the role of quinidine therapy in improving the outcome of high-risk BrS-patients. Reports have postulated an antiarrhythmic effect of other drugs in BrS (amrinone,13 bepridil,14,15 clarithromycin,13 denopamine,15 dimethyl lithospermate B,16 mexiletine,17,18 milrinone,13 phentolamine,17 prazosin,17 sotalol,19,20 tedisamil13,21 and 4-aminopyridine13). We consider the evidence to use these drugs as antiarrhythmic treatment in BrS-patients currently to be too low.

In BrS-patients an important issue regarding ventricular tachyarrhythmias is that they can present as an epileptic seizure and that the cerebral hypoperfusion may create a clinical picture easily confused with a postictal phase. Therefore, in patients with seizures both epilepsy and arrhythmia syndromes such as Brugada syndrome7 (or, e.g., Long-QT syndrome)22 are part of the differential diagnosis. Many antiepileptic drugs, such as carbamazepine or phenytoin, act through cerebral ion channel blockade but will also result in cardiac ion channel blockade.23-25 The latter may have a deleterious (and possibly fatal) effect in patients with an arrhythmia syndrome such as Brugada syndrome. Therefore it is important to exclude arrhythmia syndromes such as Brugada syndrome in patients suspected of epilepsy before a possible harmful treatment is started.

We hope that the website will be helpful to physicians who are in need of this

<p>| Table 2 | Drugs preferably avoided |</p>
<table>
<thead>
<tr>
<th>Drug category</th>
<th>Drug (generic)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmic</td>
<td>Amiodarone</td>
<td>Class IIb</td>
</tr>
<tr>
<td></td>
<td>Cibenzoline</td>
<td>Class IIb</td>
</tr>
<tr>
<td></td>
<td>Disopyramide</td>
<td>Class IIb</td>
</tr>
<tr>
<td></td>
<td>Lidocaine</td>
<td>Class IIb</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td>Class IIb</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>Class IIb</td>
</tr>
<tr>
<td>Psychotropic</td>
<td>Carbamazepine</td>
<td>Class IIb</td>
</tr>
<tr>
<td></td>
<td>Cyamemazine</td>
<td>Class IIb</td>
</tr>
<tr>
<td></td>
<td>Doxepin</td>
<td>Class IIb</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>Class IIb</td>
</tr>
<tr>
<td></td>
<td>Imipramine</td>
<td>Class IIb</td>
</tr>
<tr>
<td></td>
<td>Maprotiline</td>
<td>Class IIb</td>
</tr>
<tr>
<td></td>
<td>Perphenazine</td>
<td>Class IIb</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>Class IIb</td>
</tr>
<tr>
<td></td>
<td>Thioridazine</td>
<td>Class IIb</td>
</tr>
<tr>
<td>Antianginal</td>
<td>Diltiazem</td>
<td>Class III</td>
</tr>
<tr>
<td></td>
<td>Nicorandil</td>
<td>Class III</td>
</tr>
<tr>
<td></td>
<td>Nifedipine</td>
<td>Class III</td>
</tr>
<tr>
<td></td>
<td>Nitroglycerine</td>
<td>Class III</td>
</tr>
<tr>
<td></td>
<td>Sorbitrinitrate</td>
<td>Class III</td>
</tr>
<tr>
<td>Other</td>
<td>Dimenhydrinate</td>
<td>Class IIb</td>
</tr>
<tr>
<td></td>
<td>Edrophonium</td>
<td>Class IIb</td>
</tr>
<tr>
<td></td>
<td>Indapamide</td>
<td>Class IIb</td>
</tr>
</tbody>
</table>

Recommendation: Class I: convincing evidence/opinion; Class IIa: evidence/opinion less clear; Class IIb: conflicting evidence/opinion; Class III: very little evidence.
information and we welcome your suggestions and/or documentation on the safe or unsafe use of drugs in BrS-patients. We hope that use of the information provided on our website will prevent BrS-patients from suffering a cardiac arrest or sudden cardiac death initiated by drugs that should be avoided.

**Limitations**

The principal limitation of the association between certain drugs, BrS and arrhythmias, is the limited number of case reports and experimental studies suggesting an effect in BrS. Furthermore, BrS-patients may show conflicting results and large variability in their response to certain drugs. This response may also vary in different conditions (e.g., with or without fever, drug in therapeutic range, overdose or in combination with other drugs). Therefore, clinical decision making should be based on more than the presence or absence of a (single) association in another patient. In addition, it remains important for health care providers to recognize the active substances in medicines containing a combination of drugs, and to be aware of the drug category (e.g., many tricyclic antidepressants will be potentially proarrhythmic in BrS-patients).

**Acknowledgements**

We gratefully acknowledge Cardionetworks (non-profit organization based in The Netherlands, founded in 2007 with the aim to provide unbiased and up-to-date medical knowledge to the global community), and particularly its chair Jonas S.S.G. de Jong, MD, for hosting the website. The inspiration for the website comes from www.qtdrugs.org, which contains lists of drugs associated with the Long-QT syndrome.

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### Table 3: Potential Antiarrhythmic Drugs

<table>
<thead>
<tr>
<th>Drug category</th>
<th>Drug (generic)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmic</td>
<td>Isoproterenol / Isoprenaline(^1)(^5)(^6)(^7)(^11)(^13)(^14)*</td>
<td>Class I</td>
</tr>
<tr>
<td></td>
<td>Orciprenaline(^1)^15</td>
<td>Class IIa</td>
</tr>
<tr>
<td></td>
<td>Quinidine(^4)(^8)(^9)(^15)(^16)(^17)†</td>
<td>Class I</td>
</tr>
<tr>
<td>Other</td>
<td>Cilostazol(^11)(^18)(^19)</td>
<td>Class IIb</td>
</tr>
</tbody>
</table>

Recommendation: Class I: convincing evidence/opinion; Class IIa: evidence/opinion less clear; Class IIb: conflicting evidence/opinion.

*In adults an isoproterenol regimen of 0.003±0.003 µg/kg/min has been used by Ohgo et al.\(^15\) and 0.01 to 0.02 µg/kg/min has been used by Kasanuki et al.\(^18\)† Aim at quinidine plasma levels of 1-3 µg/mL or 3.5-11 µmol/L.

### Table 4: Diagnostic Drugs

<table>
<thead>
<tr>
<th>Drug category</th>
<th>Drug (generic)</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmic</td>
<td>Ajmaline(^2)(^6)(^6)(^7)(^9)(^25)</td>
<td>Max. 1mg/kg</td>
</tr>
<tr>
<td></td>
<td>Flecainide(^3)(^0)(^3)(^4)*</td>
<td>Max. 2mg/kg</td>
</tr>
<tr>
<td></td>
<td>Pilsicainide(^3)(^5)(^3)(^8)</td>
<td>Max. 1mg/kg</td>
</tr>
<tr>
<td></td>
<td>Procainamide(^1)(^7)(^2)(^6)(^9)(^10)(^1)</td>
<td>Max. 10mg/kg</td>
</tr>
</tbody>
</table>

* It has been reported by Wolpert et al.\(^2\) that flecainide has a 32% lower sensitivity to uncover a type-1 Brugada ECG than ajmaline; † In the first consensus report (Wilde et al.\(^2\)), the sensitivity of procainamide was considered relatively low.
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