

## DRUGS ASSOCIATED WITH QT INTERVAL PROLONGATION<sup>2-65</sup>

| Drugs by Class          | Association <sup>a</sup> | Torsadogenic <sup>b</sup> | FDA Labelling <sup>c</sup> | Comments   |
|-------------------------|--------------------------|---------------------------|----------------------------|--|
| <b>Anesthetics</b>      |                          |                           |                            |  |
| Halothane               | Probable                 | —                         | —                          | Non-specific arrhythmias reported in PI.                           |
| Isoflurane              | Probable                 | —                         | —                          |  |
| <b>Anti-arrhythmics</b> |                          |                           |                            |  |
| Amiodarone              | Definite                 | High                      | QT, TdP                    | IV affects QTc less than oral; proarrhythmia infrequent.           |
| Adenosine               | Proposed                 | —                         | —                          |  |
| Disopyramide            | Definite                 | High                      | QT, TdP                    | Rate appears lower than that of quinidine.                         |
| Flecainide              | Definite                 | —                         | QT, TdP                    | Proarrhythmia “rare.”  |
| Ibutilide               | Definite                 | High                      | QT, TdP                    | Proarrhythmia 1.7%.  |
| Procainamide            | Definite                 | High                      | QT, TdP                    | Rate appears lower than that of quinidine.                         |
| Propafenone             | Definite                 | Medium high               | QT, TdP                    | Proarrhythmia “rare.”  |
| Quinidine               | Definite                 | High                      | QT, TdP                    | “Quinidine syncope” in 2–6% of patients.                           |
| Sotalol                 | Definite                 | High                      | QT, TdP                    | Proarrhythmia ~2%.   |
| <b>Anticonvulsants</b>  |                          |                           |                            |  |
| Fosphenytoin            | Proposed                 | —                         | QT <sup>d</sup>            | No cases through MEDLINE search.                                   |
| <b>Antidepressants</b>  |                          |                           |                            |  |
| Amitriptyline           | Definite                 | Medium high               | —                          | Non-specific ECG changes reported in PI.                           |
| Citalopram              | Probable                 | —                         | —                          |  |
| Desipramine             | Definite                 | —                         | QT                         | VF, sudden death reported in PI.                                   |
| Doxepin                 | Definite                 | Medium high               | —                          |  |
| Fluoxetine              | Probable                 | —                         | QT, TdP                    | 1 in 10,000 ventricular arrhythmias reported in PI.                |
| Imipramine              | Definite                 | Medium high               | —                          | Non-specific arrhythmias reported in PI.                           |
| Maprotiline             | Definite                 | —                         | —                          | ECG changes; QRS reported in PI.                                   |
| Nortriptyline           | Definite                 | —                         | —                          | Non-specific arrhythmias reported in PI.                           |
| Paroxetine              | Probable                 | —                         | TdP                        | Lower risk than that of TCAs.                                      |
| Sertraline              | Probable                 | —                         | QT, TdP                    | Lower risk than that of TCAs.                                      |
| Venlafaxine             | Proposed                 | —                         | QT                         | 1:1000 risk of arrhythmia reported in PI.                          |
| <b>Antihistamines</b>   |                          |                           |                            |  |
| Clemastine              | Proposed                 | —                         | —                          |  |
| Diphenhydramine         | Proposed                 | —                         | —                          |  |
| Loratadine              | Proposed                 | Not clear                 | —                          | Prolongation appears unlikely.                                     |
| <b>Antiinfectives</b>   |                          |                           |                            |  |
| Clarithromycin          | Probable                 | Medium high               | QT, TdP                    |  |
| Erythromycin            | Definite                 | Medium high               | QT, TdP                    | Known drug–drug interactions with other agents (e.g. terfenadine). |

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| Fluconazole                                | Probable                 | —                         | —                          | Risk may be higher with IV dosing.                               |
| Foscarnet                                  | Proposed                 | —                         | QT                         |  |
| Ganciclovir                                | Proposed                 | —                         | —                          |  |
| Gatifloxacin                               | Probable                 | —                         | QT                         |  |
| Ketoconazole                               | Probable                 | —                         | —                          | Known drug–drug interactions with other agents (e.g. cisapride). |
| Levofloxacin                               | Proposed                 | —                         | TdP                        | Lower risk than that of similar agents.                          |
| Mefloquine                                 | Proposed                 | —                         | —                          | QT with halofantrine.  |
| Moxifloxacin                               | Probable                 | —                         | QT                         | Lower risk than that of similar agents.                          |
| Pentamidine                                | Definite                 | Medium high               | QT, TdP                    |  |
| Quinine                                    | Probable                 | Medium high               |                            |  |
| Trimethoprim-sulfamethoxazole              | Proposed                 | Low                       | —                          |  |
| <b>Antipsychotics</b>                      |                          |                           |                            |  |
| Chlorpromazine                             | Probable                 | —                         | —                          | Non-specific ECG changes and sudden death reported in PI.        |
| Clozapine                                  | Proposed                 | —                         | —                          | Non-specific ECG changes reported in PI.                         |
| Haloperidol                                | Definite                 | Medium high               | QT, TdP                    |  |
| Pimozide                                   | Definite                 | —                         | QT                         | Drug–drug interactions also lead to QT prolongation.             |
| Quetiapine                                 | Proposed                 | —                         | QT                         |  |
| Risperidone                                | Proposed                 | —                         | QT                         | Sudden death reported in PI.                                     |
| Ziprasidone                                | Definite                 | —                         | QT                         |  |
| <b>Cancer chemotherapeutic agents</b>      |                          |                           |                            |  |
| Arsenic trioxide                           | Definite                 | —                         | QT, TdP                    |  |
| Tamoxifen                                  | Probable                 | —                         | QT                         | Overdose situations.   |
| <b>Cardiovascular non-anti-arrhythmics</b> |                          |                           |                            |  |
| Indapamide                                 | Proposed                 | —                         | QT                         |  |
| Probucol                                   | Definite                 | —                         | NA                         | Removed from US market.  |
| <b>Gastrointestinal agents</b>             |                          |                           |                            |  |
| Octreotide                                 | Proposed                 | —                         | QT                         |  |
| Droperidol                                 | Definite                 | Medium high               | QT, TdP                    |  |
| Dolasetron                                 | Proposed                 | —                         | QT <sup>d</sup>            |  |
| <b>Migraine agents</b>                     |                          |                           |                            |  |
| Naratriptan                                | Probable                 | —                         | QT                         |  |
| Sumatriptan                                | Probable                 | —                         | QT                         |  |
| Rizatriptan                                | Probable                 | —                         | —                          | 1:1000 risk of arrhythmia.                                       |
| Zolmitriptan                               | Probable                 | —                         | QT                         |  |

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|-----------------------------|--------------------------|---------------------------|----------------------------|----------------------------|
| <b>Miscellaneous agents</b> |                          |                           |                            |                            |
| Amantadine                  | Low                      | —                         | —                          |                            |
| Epinephrine                 | Proposed                 | —                         | —                          |                            |
| Methadone                   | Probable                 | —                         | —                          | Syncope reported in PI.    |
| Salmeterol                  | Proposed                 | —                         | QT <sup>d</sup>            |                            |
| Tacrolimus                  | Proposed                 | —                         | —                          |                            |
| Tizanidine                  | Probable                 | —                         | QT                         | 1:1000 risk of arrhythmia. |

FDA = United States Food and Drug Administration

IV = intravenous

PI = package insert

QT = QT interval prolongation

TdP = torsades de pointes

ECG = electrocardiogram

VF = ventricular fibrillation

TCA = tricyclic antidepressant

NA = not applicable

HCTZ = hydrochlorothiazide.

<sup>a</sup> Associations are based on the strength of evidence that supports whether QT prolongation can occur. This categorization does not delineate an individual patient's risk of QT prolongation.

<sup>b</sup> Torsadogenic potential is divided into four categories as characterized in a previous publication<sup>1</sup>: high = drugs that are potent blockers of currents prolonging myocardial repolarization; medium high = drugs that prolong myocardial repolarization at higher doses, or at normal doses with concurrent administration of drugs that inhibit drug metabolism; low = drugs that prolong action potential duration and QT interval at high doses or concentrations that are clearly above the therapeutic range; and not clear = drugs that block repolarizing ion currents in vitro but that have so far not been shown to prolong repolarization in other in vitro models.

<sup>c</sup> Describes whether the FDA-approved product labelling includes mention of QT prolongation, torsades de pointes, or both.<sup>2-65</sup>

<sup>d</sup> Drug reported in the product labelling to prolong the QT interval, but evidence to support such an effect is lacking or published data suggest otherwise.

- Haverkamp W, Eckardt L, Monnig G, et al. Clinical aspects of ventricular arrhythmias associated with QT prolongation. Eur Heart J 2001;3(suppl K):K81-8.
- Wyeth Ayerst. Fluothane (halothane) package insert. Philadelphia (PA); 2000.
- Baxter Pharmaceutical Products Inc. Isoflurane [generic] package insert. New Providence (NJ); 2000.
- Wyeth Laboratories. Cordarone (amiodarone) package insert. Philadelphia (PA); 1999.
- Fujisawa Healthcare, Inc. Adenocard (adenosine) package insert. Deerfield (IL); 2000.
- G. D. Searle. Norpace (disopyramide) package insert. Chicago; 1999.
- Pfizer, Inc. Tikosyn (dofetilide) package insert. New York; 1999.
- 3M Pharmaceuticals. Tambocor (flecainide) package insert. Northridge (CA); 1998.
- Pharmacia and Upjohn Company. Corvert (ibutilide) package insert. Kalamazoo (MI); 1999.
- Apothecon. Pronestyl (procainamide) package insert. Princeton (NJ); 1991.
- Knoll Pharmaceutical Company. Rythmol (propafenone) package insert. Mount Olive (NY); 1998.
- A.H. Robins Company. Quinidex Extentabs (quinidine extended release) package insert. Richmond (VA); 1998.
- Berlex Laboratories. Betapace (sotalol) package insert. Wayne (NJ); 2000.
- Parke Davis. Cerebyx (fosphenytoin) package insert, Morris Plains (NJ); 1999.
- Mylan Pharmaceuticals, Inc. Amitriptyline [generic] package insert. Morgantown (WV); November 2000.
- Forest Laboratories, Inc. Celexa (citalopram) package insert. St. Louis (MO); 2000.
- Aventis Pharmaceuticals. Norpramin (desipramine) package insert. Parsippany (NJ); 1997.
- Pfizer, Inc. Sinequan (doxepin) package insert. New York; 1996.
- Distal Products Company. Prozac (fluoxetine) package insert. Indianapolis (IN); 2001.
- Geneva Pharmaceuticals, Inc. Imipramine [generic] package insert. Broomfield (CT); 1999.
- Mylan Pharmaceuticals, Inc. Maprotiline [generic] package insert. Morgantown (WV); 2001.
- Watson Laboratories, Inc. Nortriptyline [generic] package insert. Corona (CA); 2001.

23. GlaxoSmithKline. Paxil (paroxetine) package insert. Research Triangle Park (NC); 2002.
24. Pfizer, Inc. Zoloft (sertraline) package insert. New York; 2001.
25. Wyeth Laboratories. Effexor (venlafaxine) package insert. Philadelphia (PA); 2001.
26. Geneva Pharmaceuticals, Inc. Clemastine [generic] package insert. Broomfield (CT); 2000.
27. Major Pharmaceuticals. Diphenhydramine [generic] package insert. Livonia (MI); 2001.
28. Schering Corporation. Claritin (loratadine) package insert. Kenilworth (NJ); 2000.
29. Abbott Laboratories. Biaxin (clarithromycin) package insert North Chicago (IL); 2000.
30. Abbott Laboratories. Erythromycin lactobionate i.v. [generic] package insert. North Chicago (IL); 1992.
31. Pfizer, Inc. Diflucan (fluconazole) package insert. New York; 1998.
32. AstraZeneca Pharmaceuticals LP. Foscavir (foscarnet) package insert. Wilmington (DE); 1999.
33. Roche Laboratories Inc. Cytovene (ganciclovir) package insert. Nutley (NJ); 2000.
34. Bristol-Myers Squibb. Tequin (gatifloxacin) package insert. Princeton (NJ); 2000.
35. Janssen Pharmaceutica Products. Sporanox (itraconazole capsules) package insert. Titusville (NJ); 2000.
36. Janssen Pharmaceutica Products. Sporanox (itraconazole oral solution) package insert. Titusville (NJ) ; 2000.
37. Janssen Pharmaceutica Products. Sporanox (itraconazole injection) package insert. Titusville (NJ); 2000.
38. Janssen Pharmaceutica Products. Nizoral (ketoconazole) package insert. Titusville (NJ); 1998.
39. Ortho-McNeil Pharmaceuticals. Levaquin (levofloxacin) package insert. Raritan (NJ); 2000.
40. Roche Laboratories Inc. Lariam (mefloquine) package insert. Nutley (NJ); 1999.
41. Bayer Corporation. Avelox (moxifloxacin) package insert. West Haven (CT); 2001.
42. American Pharmaceutical Partners. Nebupent (pentamidine) package insert. Los Angeles; 1999.
43. Roche Laboratories Inc. Bactrim (trimethoprim-sulfamethoxazole) package insert. Nutley (NJ); 2000.
44. GlaxoSmithKline. Thorazine (chlorpromazine) package insert. Research Triangle Park (NC); 2000.
45. Ortho-McNeil Pharmaceutical, Inc. Haldol (haloperidol) package insert. Raritan (NJ); October 1998.
46. Gate Pharmaceuticals. Orap (pimozide) package insert. Sellersville (PA); 1999.
47. AstraZeneca Pharmaceuticals LP. Seroquel (quetiapine) package insert. Wilmington (DE); 2001.
48. Janssen Pharmaceutica Products. Risperdal (risperidone) package insert. Titusville (NJ); 2000.
49. Novartis Pharmaceutical Corporation. Clozaril (clozapine) package insert. East Hanover (NJ); 2001.
50. Pfizer, Inc. Geodon (ziprasidone) package insert. New York; July 2002.
51. Cell Therapeutics, Inc. Trisenox (arsenic trioxide) package insert. Seattle (WA); 2000.
52. AstraZeneca Pharmaceuticals LP. Nolvadex (tamoxifen) package insert. Wilmington (DE); 1999.
53. Mylan Pharmaceuticals, Inc. Indapamide [generic] package insert. Morgantown (WV); 1998.
54. Novartis Pharmaceuticals Corporation. Sandostatin (octreotide) package insert. East Hanover (NJ); 1999.
55. Abbott Laboratories. Droperidol [generic] package insert. North Chicago (IL); 1995.
56. Aventis Pharmaceuticals, Inc. Anzemet (dolasetron) package insert. Kansas City (MO); 1999.
57. GlaxoSmithKline. Amerge (naratriptan) package insert. Research Triangle Park (NC); 1999.
58. GlaxoSmithKline. Imitrex (sumatriptan) package insert. Research Triangle Park (NC); 2001.
59. Merck and Co., Inc. Maxalt (rizatriptan) package insert. West Point (PA); 2000.
60. AstraZeneca Pharmaceuticals LP. Zomig (zolmitriptan) package insert. Wilmington (DE); 2000.
61. American Regent Laboratories, Inc. Epinephrine [generic] package insert. Shirley (NY); June 1999.
62. Roxane Laboratories, Inc. Dolophine (methadone) package insert. Columbus (OH); 2001.
63. GlaxoSmithKline. Serevent (salmeterol) package insert. Research Triangle Park (NC); 2000.
64. Fujisawa Healthcare, Inc. Prograf (tacrolimus) package insert. Deerfield Park (IL); 2001.
65. Elan Pharmaceuticals Inc. Zanaflex (tizanidine) package insert. South San Francisco (CA); 2000.

Adapted from Clinical relevance and management of drug-related QT interval prolongation. *Pharmacotherapy*. 2003;23(7):881–908. (Drugs not available in Canada have been removed from this table.)