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References

Depression and anxiety disorders CHAPTER 3 Summary ■ ■ Tricyclics (but not lofepramine) have an established link to ion channel blockade and cardiac arrhythmia, especially in overdose. ■ ■ Non-tricyclics generally have a very low risk of inducing arrhythmia. ■ ■ Sertraline is recommended post MI, but other SSRIs and mirtazapine are also likely to be safe. ■ ■ Bupropion, citalopram, escitalopram, moclobemide and venlafaxine should be used with caution or avoided in those at risk of serious arrhythmia (those with heart failure, left ventricular hypertrophy, previous arrhythmia or MI). An ECG should be performed at baseline and 1 week after every increase in dose if any of these drugs are used in at-risk patients. ■ ■ TCAs (with the exception of lofepramine) are best avoided completely in patients at risk of serious arrhythmia. If use of a TCA cannot be avoided, an ECG should be performed at baseline, 1 week after each increase in dose and periodically throughout treatment. Frequency will be determined by the stability of the cardiac disorder. Advice from a cardiology specialist should be sought. ■ ■ The arrhythmogenic potential of TCAs and other antidepressants is dose related. Consideration should be given to ECG monitoring of all patients prescribed doses towards the top of the licensed range and those who are prescribed other drugs that, through pharmacokinetic (e.g. fluoxetine) or pharmacodynamic (e.g. diuretics) mechanisms, may add to the risk posed by the drug. References

1. Taylor D. Antidepressant drugs and cardiovascular pathology: a clinical overview of effectiveness and safety. *Acta Psychiatr Scand* 2008; 118:434-442.
2. Whang W, et al. Depression and risk of sudden cardiac death and coronary heart disease in women: results from the Nurses' Health Study. *J Am Coll Cardiol* 2009; 53:950-958.
3. Nemeroff CB, et al. Heartache and heartbreak: the link between depression and cardiovascular disease. *Nat Rev Cardiol* 2012; 9:526-539.
4. Thanacoody HK, et al. Tricyclic antidepressant poisoning: cardiovascular toxicity. *Toxicol Rev* 2005; 24:205-214.
5. Sicouri S, et al. Sudden cardiac death secondary to antidepressant and antipsychotic drugs. *Expert Opin Drug Saf* 2008; 7:181-194.
6. Weeke P, et al. Antidepressant use and risk of out-of-hospital cardiac arrest: a nationwide case-time-control study. *Clin Pharmacol Ther* 2012; 92:72-79.
7. Leonard CE, et al. Antidepressants and the risk of sudden cardiac death and ventricular arrhythmia. *Pharmacoepidemiol Drug Saf* 2011; 20:903-913.
8. Hong HK, et al. Block of the human ether-a-go-go-related gene (hERG) K⁺ channel by the antidepressant desipramine. *Biochem Biophys Res Commun* 2010; 394:536-541.
9. Coupland C, et al. Antidepressant use and risk of cardiovascular outcomes in people aged 20 to 64: cohort study using primary care database. *BMJ* 2016; 352:i1350.

10. Prasitlumkum N, et al. Antidepressants and risk of sudden cardiac death: a network meta-analysis and systematic review. *Med Sci (Basel)* 2021; 9:26.
11. Khalifa M, et al. Mechanism of sodium channel block by venlafaxine in guinea pig ventricular myocytes. *J Pharmacol Exp Ther* 1999; 291:280-284.
12. Colbridge MG, et al. Venlafaxine in overdose: experience of the National Poisons Information Service (London centre). *J Toxicol Clin Toxicol* 1999; 37:383.
13. Blythe D, et al. Cardiovascular and neurological toxicity of venlafaxine. *Hum Exp Toxicol* 1999; 18:309-313.
14. Combes A, et al. Conduction disturbances associated with venlafaxine. *Ann Intern Med* 2001; 134:166-167.
15. Isbister GK. Electrocardiogram changes and arrhythmias in venlafaxine overdose. *Br J Clin Pharmacol* 2009; 67:572-576.
16. Whyte IM, et al. Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants. *QJM* 2003; 96:369-374.
17. Feighner JP. Cardiovascular safety in depressed patients: focus on venlafaxine. *J Clin Psychiatry* 1995; 56:574-579.
18. Abbas R, et al. Lack of an effect of supratherapeutic dose of venlafaxine on cardiac repolarization in healthy subjects. *Clin Pharmacol Drug Dev* 2022; 11:100-111.

414 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 3 19. Martinez C, et al. Use of venlafaxine compared with other antidepressants and the risk of sudden cardiac death or near death: a nested case-control study. *BMJ* 2010; 340:c249. 20. Cooper JM, et al. Desvenlafaxine overdose and the occurrence of serotonin toxicity, seizures and cardiovascular effects. *Clin Toxicol (Phila)* 2017; 55:18-24. 21. Downes MA, et al. QTc abnormalities in deliberate self-poisoning with moclobemide. *Intern Med J* 2005; 35:388-391. 22. Kelly CA, et al. Comparative toxicity of citalopram and the newer antidepressants after overdose. *J Toxicol Clin Toxicol* 2004; 42:67-71. 23. Grundemar L, et al. Symptoms and signs of severe citalopram overdose. *Lancet* 1997; 349:1602. 24. Mohammed R, et al. Prolonged QTc interval due to escitalopram overdose. *J Miss State Med Assoc* 2010; 51:350-353. 25. Isbister GK, et al. Bupropion overdose: QTc prolongation and its clinical significance. *Ann Pharmacother* 2003; 37:999-1002. 26. Service JA, et al. QT prolongation and delayed atrioventricular conduction caused by acute ingestion of trazodone. *Clin Toxicol (Phila)* 2008; 46:71-73. 27. Dattilo PB, et al. Prolonged QT associated with an overdose of trazodone. *J Clin Psychiatry* 2007; 68:1309-1310. 28. de Boer RA, et al. QT interval prolongation after sertraline overdose: a case report. *BMC Emerg Med* 2005; 5:5. 29. Abbas R, et al. A thorough QT study to evaluate the effects of a supratherapeutic dose of sertraline on cardiac repolarization in healthy subjects. *Clin Pharmacol Drug Dev* 2020; 9:307-320. 30. Maljuric NM, et al. Use of selective serotonin re-uptake inhibitors and the heart rate corrected QT interval in a real-life setting: the population-based Rotterdam Study. *Br J Clin Pharmacol* 2015; 80:698-705. 31. van Haelst IM, et al. QT interval prolongation in users of selective serotonin reuptake inhibitors in an elderly surgical population: a cross-sectional study. *J Clin Psychiatry* 2014; 75:15-21. 32. Beach SR, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. *J Clin Psychiatry* 2014; 75:e441-449. 33. Castro VM, et al. QT interval and antidepressant use: a cross sectional study of electronic health records. *BMJ* 2013; 346:f288. 34. Zivin K, et al. Evaluation of the FDA warning against prescribing citalopram at doses exceeding 40 mg. *Am J Psychiatry* 2013; 170:642-650. 35. Ray WA, et al. High-dose citalopram and escitalopram and the risk of out-of-hospital death. *J Clin Psychiatry* 2017; 78:190-195. 36. Lin YT, et al. Selective serotonin reuptake

inhibitor use and risk of arrhythmia: a nationwide, population-based cohort study. *Clin Ther* 2019; 41:1128–1138.e8. 37. Farhat H, et al. Citalopram and escitalopram: mechanisms of cardiotoxicity, toxicology predisposition and risks of use in geriatric and hemodialysis populations. *Glob Cardiol Sci Pract* 2024; 2024:e202434. 38. Faraj P, et al. Pro-arrhythmic effect of escitalopram and citalopram at serum concentrations commonly observed in older patients: a study based on a cohort of 19,742 patients. *EBioMedicine* 2023; 95:104779. 39. Dubovsky SL. Pharmacokinetic evaluation of vortioxetine for the treatment of major depressive disorder. *Expert Opin Drug Metab Toxicol* 2014; 10:759–766. 40. Alam MY, et al. Safety, tolerability, and efficacy of vortioxetine (Lu AA21004) in major depressive disorder: results of an open-label, flexible- dose, 52-week extension study. *Int Clin Psychopharmacol* 2014; 29:36–44. 41. Wang Y, et al. Effect of vortioxetine on cardiac repolarization in healthy adult male subjects: results of a thorough QT/QTc study. *Clin Pharmacol Drug Dev* 2013; 2:298–309. 42. Donazzolo Y, et al. Evaluation of the effects of therapeutic and supra-therapeutic doses of agomelatine on the QT/QTc interval: a phase I, randomised, double--blind, placebo-controlled and positive-controlled, cross-over thorough QT/QTc study conducted in healthy volunteers. *J Cardiovasc Pharmacol* 2014; 64:440–451. 43. Edwards J, et al. Vilazodone lacks proarrhythmogenic potential in healthy participants: a thorough ECG study. *Int J Clin Pharmacol Ther* 2013; 51:456–465. 44. Mago R, et al. Safety and tolerability of levomilnacipran ER in major depressive disorder: results from an open-label, 48-week extension study. *Clin Drug Investig* 2013; 33:761–771. 45. Periclou A, et al. Effects of milnacipran on cardiac repolarization in healthy participants. *J Clin Pharmacol* 2010; 50:422–433. 46. Glassman AH, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA* 2002; 288:701–709. 47. van Melle JP, et al. Effects of antidepressant treatment following myocardial infarction. *Br J Psychiatry* 2007; 190:460–466. 48. Strik JJ, et al. Efficacy and safety of fluoxetine in the treatment of patients with major depression after first myocardial infarction: findings from a double-blind, placebo-controlled trial. *Psychosom Med* 2000; 62:783–789. 49. Rigotti NA, et al. Bupropion for smokers hospitalized with acute cardiovascular disease. *Am J Med* 2006; 119:1080–1087. 50. Alqdwah-Fattouh R, et al. Differential effects of antidepressant subgroups on risk of acute myocardial infarction: a nested case-control study. *Br J Clin Pharmacol* 2020; 86:2040–2050. 51. Wu CS, et al. Use of antidepressants and risk of hospitalization for acute myocardial infarction: a nationwide case-crossover study. *J Psychiatr Res* 2017; 94:7–14. 52. Lesperance F, et al. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. *JAMA* 2007; 297:367–379. 53. Astrom--Lilja C, et al. Drug-induced torsades de pointes: a review of the Swedish pharmacovigilance database. *Pharmacoepidemiol Drug Saf* 2008; 17:587–592. 54. Angermann CE, et al. Effect of escitalopram on all-cause mortality and hospitalization in patients with heart failure and depression: the MOOD-HF randomized clinical trial. *JAMA* 2016; 315:2683–2693. 55. Hedrick R, et al. The impact of antidepressants on depressive symptom severity, quality of life, morbidity, and mortality in heart failure: a systematic review. *Drugs Context* 2020; 9:2020-5-4.

Depression and anxiety disorders CHAPTER 3 56. Sherwood A, et al. Effects of exercise and sertraline on measures of coronary heart disease risk in patients with major depression: results from the SMILE-II randomized clinical trial. *Psychosom Med* 2016; 78:602–609. 57. Wang Z, et al. Exploring the correlation between cardiovascular adverse events and antidepressant use: a retrospective pharmacovigilance analysis based on the FDA Adverse Event Reporting System database. *J Affect Disord* 2024; 367:96–108. 58. Yokohara S, et al. Psychotherapeutic drug-induced life-threatening arrhythmias: a retrospective analysis using the Japanese adverse drug event report

database. *J Arrhythm* 2023; 39:928–936. 59. Cao Y, et al. Associations of antidepressants with atrial fibrillation and ventricular arrhythmias: a systematic review and meta-analysis. *Front Cardiovasc Med* 2022; 9:840452. 60. Biffi A, et al. Antidepressants and the risk of arrhythmia in elderly affected by a previous cardiovascular disease: a real-life investigation from Italy. *Eur J Clin Pharmacol* 2018; 74:119–129. 61. Aakjaer M, et al. Serious arrhythmia in initiators of citalopram, escitalopram, and other selective serotonin reuptake inhibitors: a population- based cohort study in older adults. *Clin Transl Sci* 2022; 15:2105–2115. 62. Crome P. The toxicity of drugs used for suicide. *Acta Psychiatr Scand Suppl* 1993; 371:33–37. 63. Cheeta S, et al. Antidepressant-related deaths and antidepressant prescriptions in England and Wales, 1998–2000. *Br J Psychiatry* 2004; 184:41–47. 64. Buckley NA, et al. Fatal toxicity of serotonergic and other antidepressant drugs: analysis of United Kingdom mortality data. *BMJ* 2002; 325:1332–1333. 65. Buckley NA, et al. Greater toxicity in overdose of dothiepin than of other tricyclic antidepressants. *Lancet* 1994; 343:159–162. 66. Morgan O, et al. Fatal toxicity of antidepressants in England and Wales, 1993–2002. *Health Stat Q* 2004; (23):18–24. 67. Taylor D, et al. The cardiovascular safety of tricyclic antidepressants in overdose and in clinical use. *Ther Adv Psychopharmacol* 2024; 14:20451253241243297. 68. Egberts ACG, et al. Channeling of three newly introduced antidepressants to patients not responding satisfactorily to previous treatment. *J Clin Psychopharmacol* 1997; 17:149–155. 69. Mines D, et al. Prevalence of risk factors for suicide in patients prescribed venlafaxine, fluoxetine, and citalopram. *Pharmacoepidemiol Drug Saf* 2005; 14:367–372. 70. Chan AN, et al. A comparison of venlafaxine and SSRIs in deliberate self-poisoning. *J Med Toxicol* 2010; 6:116–121. 71. Hasnain M, et al. Escitalopram and QTc prolongation. *J Psychiatry Neurosci* 2013; 38:E11.

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