QTc Prolongation And Extrapyramidal Adverse Effects – Cause For Concern?

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Content

- What is the evidence for current anti-emetics?
- Prolonged QTc
- Extrapyramidal side effects
- Summary

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What is the evidence for therapeutic benefit of common anti-emetics?

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Haloperidol

- Incomplete evidence from published RCTs to determine the effectiveness of haloperidol for nausea and vomiting in palliative care
- Evidence largely derived from post-surgery, radiotherapy and chemotherapy

  Murray-Brown F, Dorman S.
  Haloperidol for the treatment of nausea and vomiting in palliative care patients.
  Cochrane Database Syst Rev. 2015 Nov 2;2015(11):CD006271

- Prospective, multicenter, consecutive case series. Data collected for 150 patients with moderate/ severe nausea
- At 48 hours, 114 patients (79%) had complete resolution

  Digges M, Hussein A, Wilcock A, Crawford GB, Boland JW, Agar MR, Sinnarajah A, Currow DC, Johnson MJ.
  Pharmacovigilance in Hospice/Palliative Care: Net Effect of Haloperidol for Nausea or Vomiting.
  J Palliat Med. 2018 Jan;21(1):37-43

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Olanzapine

- Theoretically interesting because of receptor and tolerance profile
- Studies scarce with low statistical power: limited evidence

  Saudemont G, Prod'Homme C, Da Silva A, Villet S, Reich M, Penel N, Gamblin V.
  The use of olanzapine as an antiemetic in palliative medicine: a systematic review of the literature.
  BMC Palliat Care. 2020 Apr 22;19(1):56

- Moderate-quality evidence that oral olanzapine probably increases the likelihood of not being nauseous or vomiting during chemotherapy from 25% to 50% in adults with solid tumours

  Sutherland A, Naessens K, Plugge E, Ware L, Head K, Burton MJ, Wee B. Olanzapine for the prevention and treatment of cancer-related nausea and vomiting in adults. Cochrane Database Syst Rev. 2018 Sep 21;9(9):CD012555

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Levomepromazine

- No published RCTs
- further studies of levomepromazine and other antiemetic agents are needed to provide better evidence for their use in this setting

Cox L, Darvill E, Dorman S.
Levomepromazine for nausea and vomiting in palliative care.
Cochrane Database Syst Rev. 2015 Nov 2;2015(11):CD009420

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Metoclopramide

Has the best trial evidence of current anti-emetics in advanced cancer showing effectiveness

Bruera ED, MacEachern TJ, Spachynski KA et al (1994) Comparison of the efficacy, safety, and pharmacokinetics of controlled release and immediate release metoclopramide for the management of chronic nausea in patients with advanced cancer. Cancer 74(12):3204–3211

Bruera E, Belzile M, Neumann C, Harsanyi Z, Babul N, Darke A (2000) A double-blind, crossover study of controlled-release metoclopramide and placebo for the chronic nausea and dyspepsia of advanced cancer. J Pain Symptom Manag 19(6):427–435

Bruera E, Moyano JR, Sala R et al (2004) Dexamethasone in addition to metoclopramide for chronic nausea in patients with advanced cancer: a randomized controlled trial. J Pain Symptom Manag 28(4):381–388

Corli O, Cozzolino A, Battaiotto L (1995) Effectiveness of levosulpiride versus metoclopramide for nausea and vomiting in advanced cancer patients: a double-blind, randomized, crossover study. J Pain Symptom Manag 10(7):521–526

Mystakidou K, Befon S, Trifyllis J, Liossi C, Papadimitriou J (1997) Tropisetron versus metoclopramide in the control of emesis in far-advanced cancer. Oncologist 2(5):319–323

Mystakidou K, Befon S, Liossi C, Vlachos L (1998) Comparison of the efficacy and safety of tropisetron, metoclopramide, and chlorpromazine in the treatment of emesis associated with far advanced cancer. Cancer 83(6):1214–1223

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MASCC/ESMO consensus recommendations: Management of nausea & vomiting in advanced cancer

- The evidence base in this field is minimal with largely poor quality trials or uncontrolled trials and case studies.
- The level of evidence in most studies is low.
- The drug of choice for managing N & V in advanced cancer is metoclopramide titrated to effect. Alternative options include haloperidol, levomepromazine, or olanzapine.

Walsh D, Davis M, Ripamonti C, Bruera E, Davies A, Molassiotis A.
2016 Updated MASCC/ESMO consensus recommendations: Management of nausea and vomiting in advanced cancer.
Support Care Cancer. 2017 Jan;25(1):333-340

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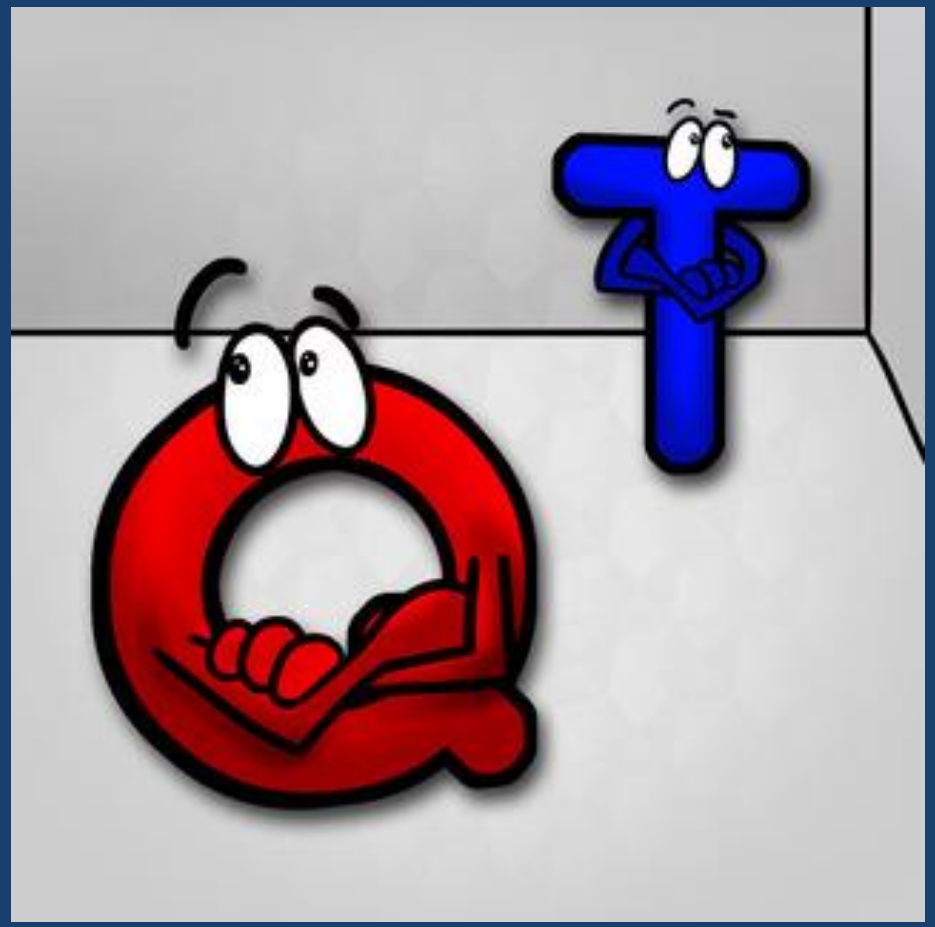

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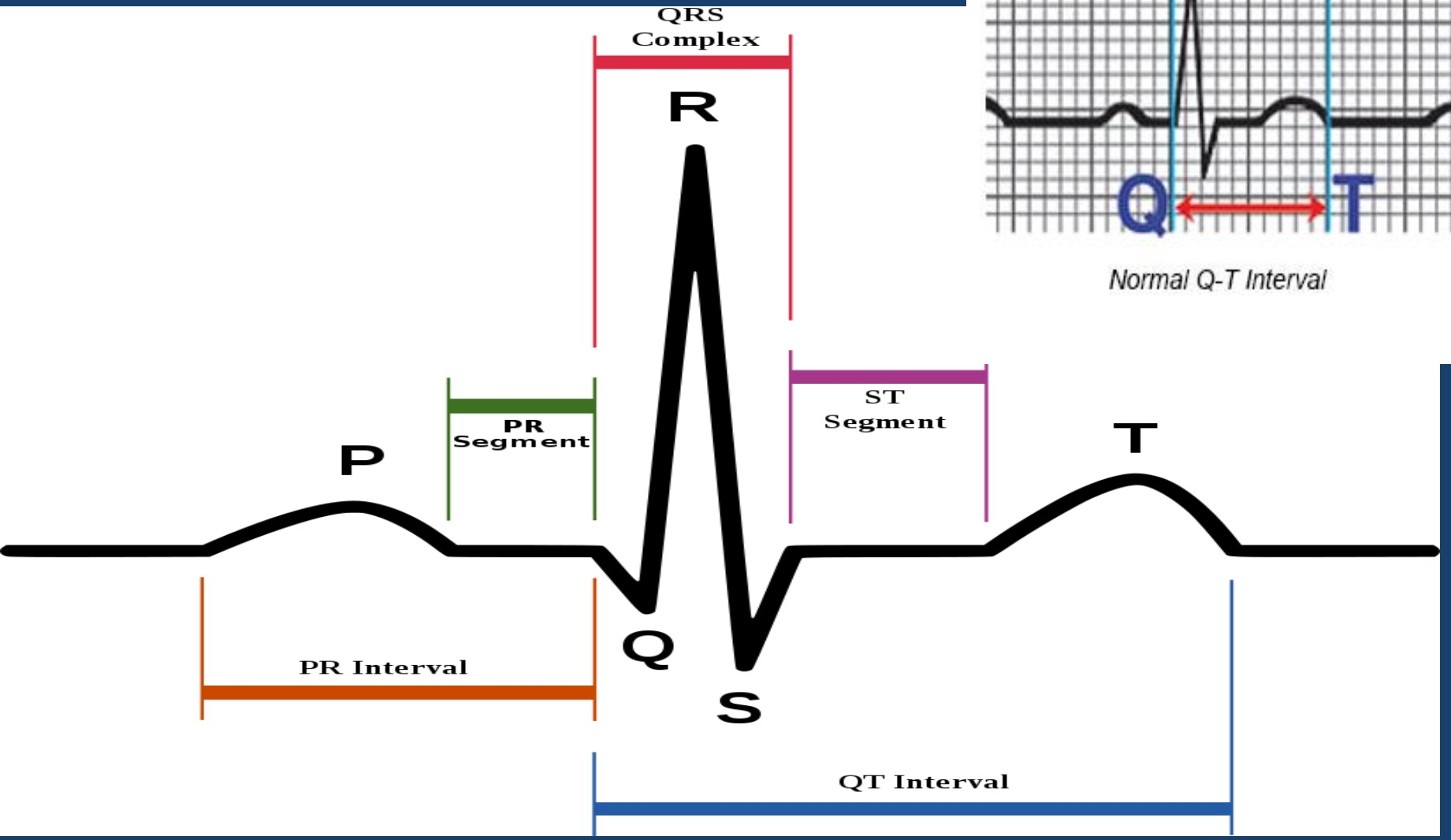
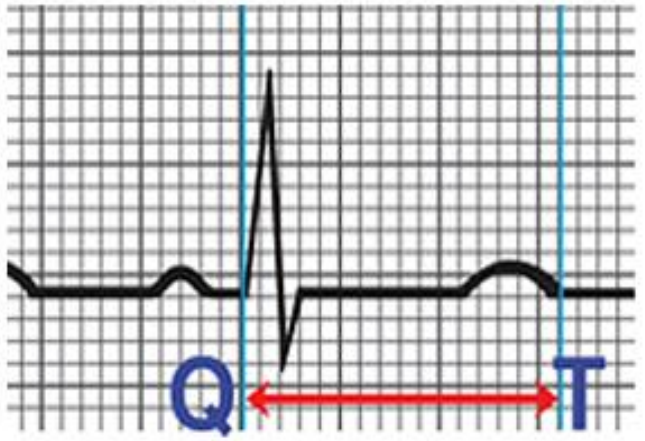


Normal Q-T Interval



Long Q-T Interval

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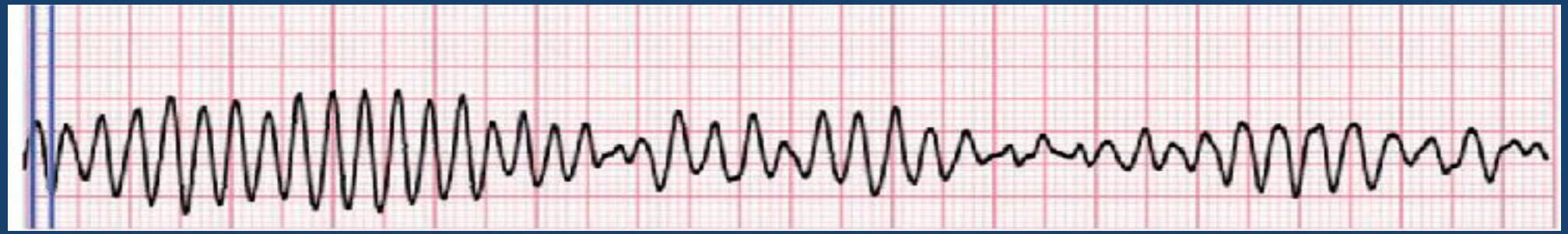
QTc Prolongation

- QT interval varies with heart rates. QTc corrects for this

Formulas for measuring QTc	Formula specifics
Bazett	$QT/\sqrt{RR}$
Fridericia	$QT/\sqrt[3]{RR}$
Framingham	$QT + 0.154 \times (1 - RR)$
Hodges	$QT + 1.75 \times (HR - 60)$

Kaye, A. et al.
QT interval abnormalities: risk factors and perioperative management in long QT syndromes and Torsades de Pointes. Journal of Anesthesia 27 (2013): 575-587

- Prolonged QT can develop in to Torsade de Pointes



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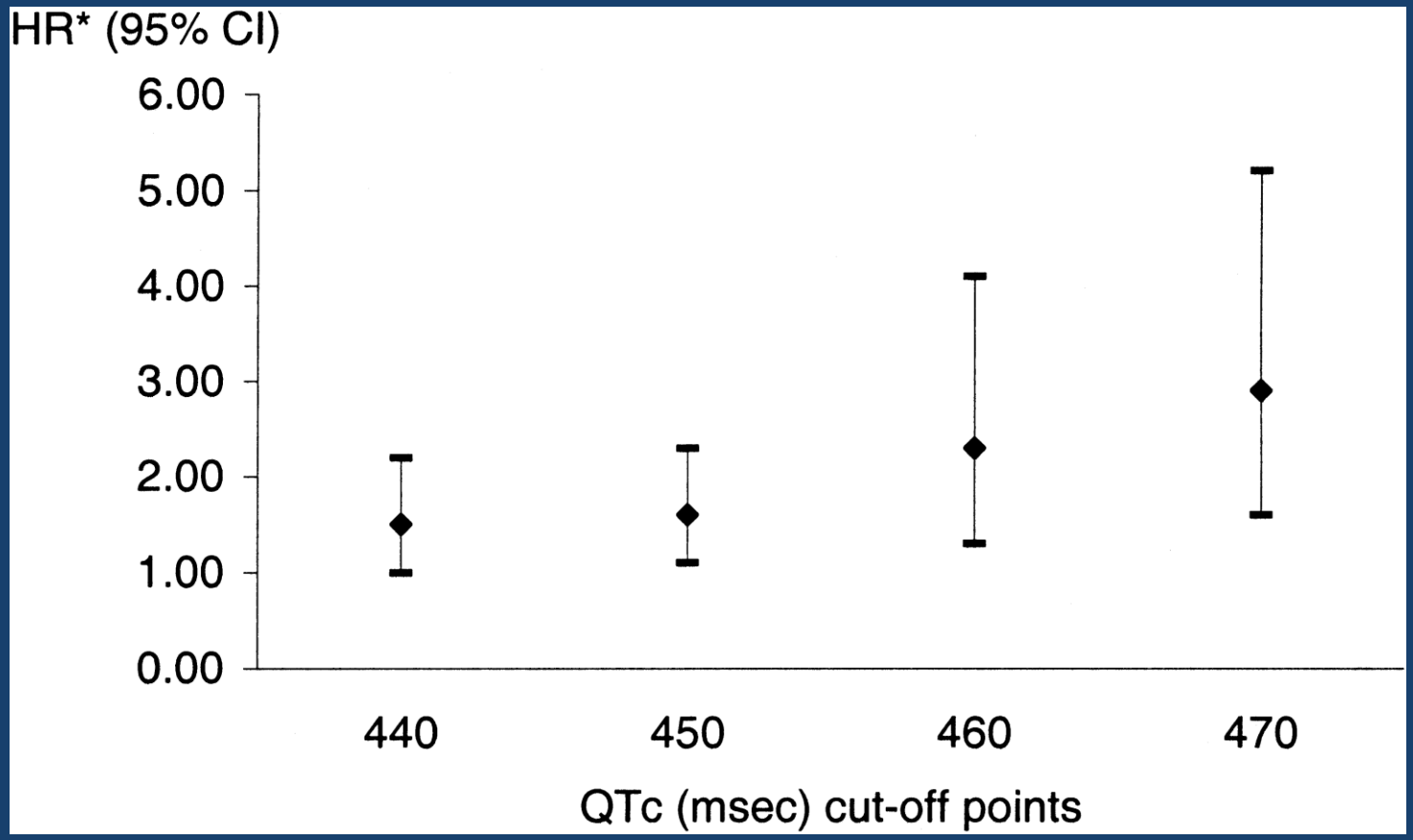
Risk of sudden death increases with QTc



Risk of sudden cardiac death (SCD) at different heart rate corrected QT (QTc) interval cutoff points.

*Adjusted for age, gender, body mass index, cholesterol/high-density lipoprotein ratio, smoking, hypertension, diabetes, myocardial infarction, and heart rate.

CI = confidence interval; HR = hazard ratio.

Sabine et al.
Prolonged QTc Interval and Risk of Sudden Cardiac Death in a Population of Older Adults.
Journal of the American College of Cardiology 47; 2 (2006): 362-367

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Do we need to worry about a prolonged QT in clinical practice?

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Risk Factors: QTc prolongation

Vandael, E., Vandenberk, B., Vandenberghe, J. et al. Risk factors for QTc-prolongation: systematic review of the evidence. Int J Clin Pharm 39 (2017): 16–25

Very Strong Evidence +++	Hypovolaemia CVS meds: diuretics, antiarrhythmic drugs QT drugs list 1: CredibleMeds
Strong Evidence ++	Age>=65 Female Smoking Ischaemic cardiomyopathy, Hypertension, Arrthymia Thyroid disturbances Hypocalcaemia >1 QTc prolonging drugs
Moderate Evidence +	Body Mass Index Prolonged QTc on baseline ECG CVS Meds: aspirin, warfarin, antihypertensives Septic shock Liver failure Charlson comorbidity index Hypochloraemia, hyponatraemia
Low Evidence -	Hyperlipidaemia Neurological disorders Diabetes Renal failure Depression

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Crediblemeds.org classification of medications according to QT prolongation risk

Drug class	Of concern: known risk of QT prolongation	Conditional (under certain conditions or in presence of risk factors) or possible risk of QT prolongation	Drugs less likely to cause QT prolongation
ANTI-EMETICS	**HALOPERIDOL DOMPERIDONE ONDANSETRON LEVOMEPROMAZINE CHLORPROMAZINE**	**METOCLOPRAMIDE OLANZAPINE PROCHLORPERAZINE MIRTAZAPINE PROMETHIAZINE**	**CYCLIZINE**
Opioids	Methadone	Buprenorphine Tramadol	Morphine/ Codeine Hydromorphone/ Oxycodone/ Fentanyl
Analgesic Adjuvants		Tricyclic antidepressants	Gabapentin/ Pregabalin NSAIDS/ Valproate Carbamazepine/ Clonidine/ Ketamine
Psychotropics	Haloperidol/Droperidol/ Levomepromazine/ Citalopram/ Escitalopram	Mirtazapine/ Fluoxetine/ Sertraline/ Paroxetine/ Venlafaxine	Lorazepam/ Clonazepam/ Midazolam/ Fluoxetine

Numbers in a Palliative Care population

	Normal QTc	Prolonged QTc >450ms (males) >470ms (females)	Prolonged QT >500ms
Number (%) of patients	**253 (84.3)**	**47 (15.7)**	**2 (0.7)**
Number (%) using a suspect drug:			
Tricyclic antidepressants	34 (13)	5 (11)	–
Phenothiazines	49 (19)	9 (19)	–
Other suspect drug	28 (11)	7 (15)	1
Total (%) using a suspect drug	82 (32)	18 (38)	1
Number (%) with cardiac disease[a]	58 (23)	17 (36)	2 (100)

Walker G, Wilcock A, Carey AM, Manderson C, Weller R, Crosby V. Prolongation of the QT interval in palliative care patients. J Pain Symptom Manage. 26(3) (2003): 855-9.

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Table 2

Medication Taken by Those With a Prolonged QTc Reading vs. Those Without (Using Gender-Specific Norms on Manual Readings)

	Normal QTc ($N = 317$)	Prolonged QTc ($N = 72$)		Total ($N = 389$)
Medication	n (%)		P	n (%)
Total using any at-risk drug	180 (56.4)	38 (54.3)	0.791	218 (56.0)
Antipsychotics	44 (13.9)	9 (12.5)	0.851	53 (13.6)
Opioids	230 (72.6)	42 (58.3)	0.022	272 (69.9)
Methadone[a]	22 (6.9)	3 (4.2)	0.594	25 (6.4)

QTc = QT interval corrected for heart rate.
[a]Daily dose range: 2.5–150 mg; median dose: 20 mg.

Hardy JR, Bundock D, Cross J, Gibbons K, Pinkerton R, Kindl K, Good P, Philip J.
Prevalence of QTc Prolongation in Patients With Advanced Cancer Receiving Palliative Care-A Cause for Concern?
J Pain Symptom Manage 2020;59(4): 856-863

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Haloperidol

- Literature review: 32 publications
- 2001-2004: significant QTc prolongation after haloperidol use
- 2006-2018: no significant QTc prolongation after haloperidol use
- Older studies used much higher doses of haloperidol compared to more recent studies (1-5mg/ 24hrs)

Burbuqe, I., Boettger, S., Schubert, M., Bettex, D., & Rudiger, A. (2020).
QTc prolongation after haloperidol administration in critically ill patients post cardiovascular surgery: A cohort study and review of the literature.
Palliative and Supportive Care, 18(4), 447-459

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Author (Reference)	Population (Number of patients, setting)	Haloperidol (Dose, administration)	Main findings
(Harvey et al., 2004) Intramuscular haloperidol or lorazepam and QT intervals in schizophrenia[a,b]	Schizophrenic patients, treated with haloperidol or lorazepam ($n = 12$ per group), blinded, randomized, placebo-controlled crossover design, emergency services	7.5 mg haloperidol im or 4 mg lorazepam im	- Haloperidol increased the QTc an average of 5.1 ms using Bazett's correction - Effects of lorazepam on QTc were nullified by correction for the heart rate elevation
(Harrigan et al., 2004) A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition[a,b,c]	Prospective, randomized study, in which patients with psychotic disorders reached steady-state, haloperidol ($n = 27$), thioridazine ($n = 30$), ziprasidone ($n = 31$), quetiapine ($n = 27$), olanzapine ($n = 24$), and risperidone ($n = 25$). QTc interval at the time of estimated peak plasma/serum concentrations in the absence and presence of metabolic inhibition	15 mg/d haloperidol po, thioridazine 300 mg/d po, ziprasidone 160 mg/d po, quetiapine 750 mg/d po, olanzapine 20 mg/d po, risperidone 6–8 mg/d increased to 16 mg/d po. ECGs were done at steady-state on monotherapy and after concomitant administration of appropriate cytochrome P450 (CYP450) inhibitors	- The presence of metabolic inhibition did not significantly augment QTc prolongation associated with any agent - Each of the antipsychotics studied was associated with measurable QTc prolongation at steady-state peak plasma concentrations, which was not augmented by metabolic inhibition - Haloperidol was associated with mean changes of 7.1 ms in QTc - No patient had a QTc interval ≥ 500 ms - Mean QTc changes from baseline were similar in the presence of metabolic inhibition to those changes observed during monotherapy
(Lindborg et al., 2003) Effects of intamuscular olanzapine vs. haloperidol and placebo on QTc intervals in acutely agitated patients[a,b,c]	Four double-blind trials were compared. Databases included: placebo-controlled, haloperidol-controlled, and geriatric placebo-controlled patients with schizophrenia ($n = 482$)	Haloperidol 7 mg im, vs. placebo im, or olanzapine im 2.5, 5, 7.5, or 10 mg	- The report showed that for acutely agitated patients with schizophrenia, bipolar mania and dementia, QTc interval changes during treatment with the newly developed intramuscular formulation of olanzapine were no greater than during treatment with intramuscular haloperidol or intramuscular placebo
(Desai et al., 2003a) Variability of heart rate correction methods for the QT interval[a,c]	Randomized, double-blind, placebo-controlled, crossover trial, healthy subjects ($n = 16$) to compare the variability of heart rate-corrected QT intervals (QTc) using different methods in a study of low-dose oral haloperidol	Single doses of haloperidol 10 mg po. Heart rate correction of the QT interval was performed using Bazett's, Fridericia's and subject-specific correction methods	- Haloperidol caused a statistically significant mean QTc prolongation using the three correction methods - At 10 h post-haloperidol administration, the mean QTc on haloperidol was 425.4 ms and was statistically significantly greater than the mean QTc on the placebo of 403.1 ms using Bazett's correction
(Desai et al., 2003b) Pharmacokinetics and QT interval pharmacodynamics of oral haloperidol in poor and extensive metabolizers of CYP2D6[a]	Randomized, double-blind, placebo-controlled, crossover trial of healthy poor (PMs) and extensive (EMs) metabolizers of CYP2D6 ($n = 16$)	Single 10 mg dose of haloperidol po	- There was a statistically significantly greater mean QTc on haloperidol 421.6 ± 20.1 ms than on placebo 408.4 ± 18.5 ms
(Su et al., 2003) A pilot crossover design study on QTc interval prolongation associated with sulpiride and haloperidol[a,b]	Four-week, crossover study to evaluate QTc intervals in patients with schizophrenia during drug-free, sulpiride-treated, and haloperidol-treated periods	Patients received 15 mg/kg of body weight of sulpiride in divided dosing for two weeks and the received 0.25 mg/kg of body weight of haloperidol in divided dosing for another two weeks	- QTc intervals in the sulpiride-treated period lengthened significantly when compared with drug-free and haloperidol-treated periods - All cases in this study were under therapeutic dose of haloperidol, and there was no significant QTc prolongation
(Kane et al., 2002) Efficacy and safety of aripiprazole and haloperidol vs. placebo in patients with schizophrenia and schizoaffective disorder[b]	Patients with schizophrenia or schizoaffective disorder ($n = 414$)	Aripiprazole 15 or 30 mg/d compared to placebo 10 mg/d haloperidol as an active control	- Haloperidol was associated with significant extrapyramidal symptoms, prolongation in QTc interval and prolactin elevation at endpoint compared with placebo and compared to aripiprazole
(Czekalla et al., 2001) Analysis of the QTc interval during olanzapine treatment of patients with schizophrenia and related psychosis[a,b,c]	Four trials comparing olanzapine with placebo, haloperidol, and risperidone in acutely psychogenic patients ($n = 2,700$)	15 ± 5 mg/d haloperidol per day	- These analyses suggest that olanzapine in patients with schizophrenia and related psychoses does not contribute to QTc prolongation resulting in potentially fatal ventricular arrhythmias - There was no significant increase in QTc in the haloperidol group

Domperidone

- Meta-analysis suggests no QT prolongation at doses domperidone <30mg/ day
- a dose-dependent increase in CV event risk with a 2.1 - to 3.1-fold increase in risk at doses >30 mg/day

Bor, Serhat et al.
"A meta-analysis on the cardiac safety profile of domperidone compared to metoclopramide."
United European gastroenterology journal vol. 6,9 (2018): 1331-1346

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Approaching prolonged QTc in Palliative Care

- Key risk factors:
  - Heart disease
  - Age
  - Female
  - use of concomitant QT-prolonging medications
  - electrolyte disturbance
  - fever, and systemic inflammation can also increase the risk of life-threatening arrhythmias

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American Heart Association scientific statement

- After initiation of a drug associated with TdP, ECG signs indicative of risk for arrhythmia include:
  - an increase in QT_c from predrug baseline of 60 ms
  - marked QT_c interval prolongation >500 ms
- Recommended actions when ECG signs of impending TdP develop:
  - discontinue the offending drug
  - replace potassium
  - administer magnesium
  - consider temporary pacing to prevent bradycardia and long pauses
  - transfer the patient to a hospital unit with the highest level of ECG monitoring surveillance where immediate defibrillation is available

Drew, B et al.
"Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation."
Circulation vol. 121,8 (2010): 1047-60

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- For patients with these risk factors:
  - What is the patient's prognosis and what is the likely length of treatment?
  - Is there an alternative anti-emetic?
  - Consider risks of prolonging QTc v potential symptom benefit
  - If no alternative, use lowest possible dose and stop if not effective
  - Beware of issues leading to drug accumulation
  - Minimise other risk factors if appropriate: stop other QT prolonging medications, correct electrolyte disturbances
  - Cardiac monitoring if appropriate: baseline ECG and post treatment ECGs
  - Consent

Wong A, Keith C, Gregory H & Liew D (2020)

Palliative and Supportive Care Prescribing Considerations Around QT Prolongation Risk in the Context of COVID-19 (Coronavirus Disease 2019) Management

Journal of Pain & Palliative Care Pharmacotherapy, 34:4, 237-239

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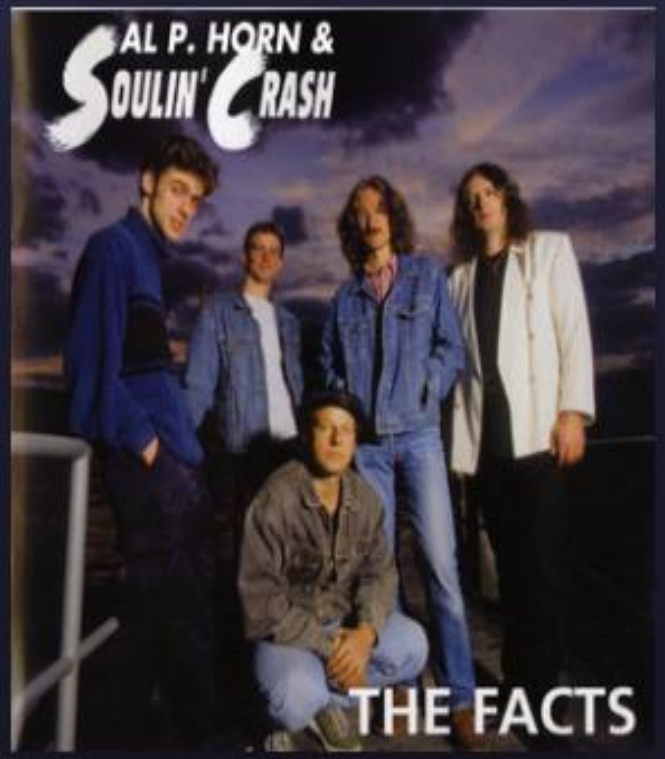

SONG

Extrapyramidal Side Effects

Alphorn • Soulin' Crash • 1999 • 2:04

What are extra-pyramidal side effects?

Spectrum of drug-induced movement disorders:

- Dystonia
- Akathisia
- Parkinsonism
- Tardive akathisia
- Tardive dyskinesia

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Dystonia

- Involuntary muscle contractions leading to abnormal posturing or repetitive movements within 48hrs of starting medication
- Can affect different areas of the body:
  - back and extremities (opisthotonus)
  - neck (torticollis)
  - jaw (trismus)
  - eyes (oculogyric crisis)
  - abdominal wall, and pelvic muscles (tortipelvic crisis)
  - facial and tongue muscles (buccolingual crisis)
  - dysphonia
  - dysphagia

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Akathasia

2 elements:

- Patient feels internally restless with a compelling urge to move
- Manifests as repetitive movements: leg crossing, swinging, or shifting from one foot to another.

Within days to weeks of starting medication

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Parkinsonism

- Resting tremor
- Muscular rigidity
- Bradykinesia: slowing of motor function in the truncal region and extremities
- Appearance: masked face, stooped posture, and a slow shuffling gait

- Occurs within days to weeks

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After 3 months of treatment

Tardive dyskinesia

- manifests as involuntary stiff jerky (choreoathetoid) movements:
  - Orofacial eg. Involuntary sticking tongue out or blinking fast
  - Limbs- less common: eg. Tapping feet, wiggling fingers
- they may impede social interaction and cause difficulty in chewing, swallowing, and talking
- worsened by anxiety

Tardive akathisia

- Urge to move that is incontrollable
- Unable to stay still: fidget all the time

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Mechanism of Action

- Antagonistic binding of dopaminergic D2 receptors
- Differences between drugs are due to binding kinetics and rates of the drug associating/dissociating with the receptor
- Efficacy of a drug may be dependent on ability to bind

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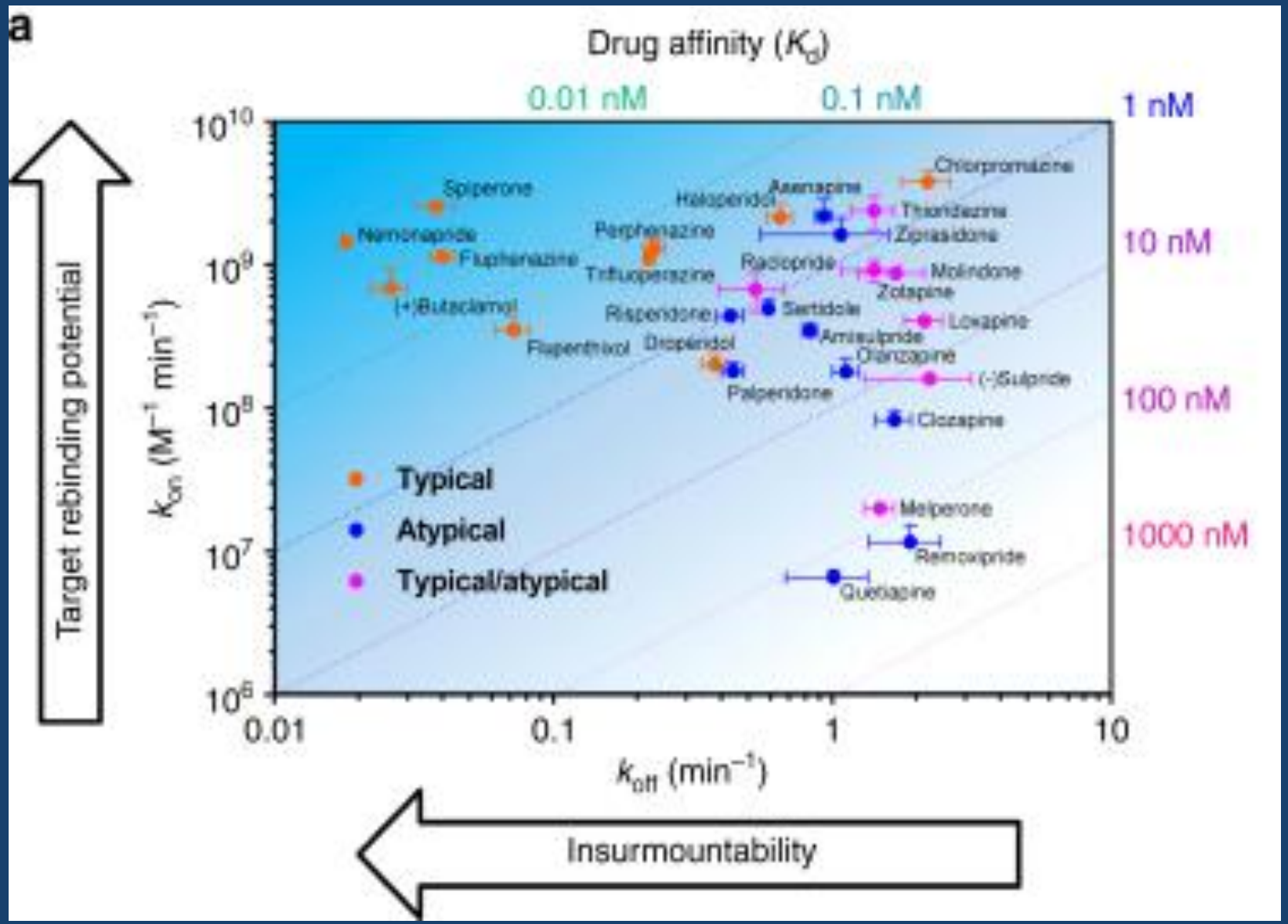
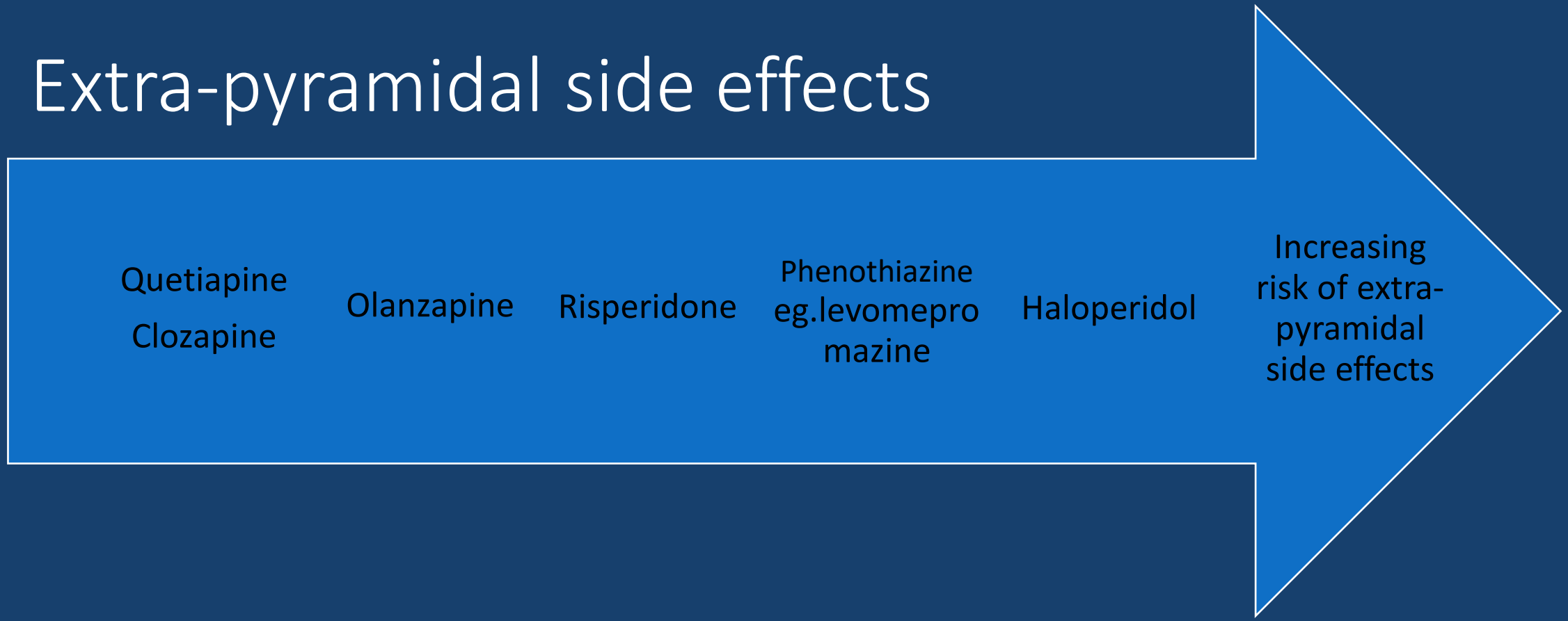
Sykes DA, Moore H, Stott L, et al.
Extrapyramidal side effects of antipsychotics are linked to their association kinetics at dopamine D_2 receptors.
Nat Commun. 2017;8(1):763



- Fast on, slow off compounds, e.g., haloperidol
- Fast on, fast off compounds, e.g., chlorpromazine
- Slow on, fast off compounds, e.g., clozapine

Extra-pyramidal side effects



Rummel-Kluge C, Komossa K, Schwarz S, et al.
Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons.
Schizophrenia Bulletin. 2012 Jan;38(1):167-177

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How common are EPS?

- Haloperidol and first generation neuroleptics: 61.6% of inpatients with chronic schizophrenia associated with EPS

  Janno S, Holi M, Tuisku K, Wahlbeck K.
  Prevalence of neuroleptic-induced movement disorders in chronic schizophrenia inpatients.
  Am J Psychiatry. 2004 Jan;161(1):160-3

- Metoclopramide (anti-emetic) 4-25%

  Ganzini L, Casey DE, Hoffman WF, McCall AL.
  The prevalence of metoclopramide-induced tardive dyskinesia and acute extrapyramidal movement disorders.
  Arch Intern Med. 1993 Jun 28;153(12):1469-75

  Parlak I, Atilla R, Cicek M, Parlak M, Erdur B, Guryay M, Sever M, Karaduman S.
  Rate of metoclopramide infusion affects the severity and incidence of akathisia.
  Emerg Med J. 2005 Sep;22(9):621-4

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Risk factors

- Prior Extrapyramidal side effects
- High medication dose

  Hedenmalm K, Güzey C, Dahl ML, Yue QY, Spigset O.

  Risk factors for extrapyramidal symptoms during treatment with selective serotonin reuptake inhibitors, including cytochrome P-450 enzyme, and serotonin and dopamine transporter and receptor polymorphisms.

  J Clin Psychopharmacol. 2006 Apr;26(2):192-7
- Elderly females are more susceptible to drug-induced parkinsonism and tardive dyskinesia

  Jeste DV. Tardive dyskinesia rates with atypical antipsychotics in older adults.

  J Clin Psychiatry. 2004;65 Suppl 9:21-4

  Salem H, Nagpal C, Pigott T, Teixeira AL. Revisiting Antipsychotic-induced Akathisia: Current Issues and Prospective Challenges.

  Curr Neuropharmacol. 2017;15(5):789-798
- Young males manifest with more dystonic reactions

  Kondo T, Otani K, Tokinaga N, Ishida M, Yasui N, Kaneko S. Characteristics and risk factors of acute dystonia in schizophrenic patients treated with nemonapride, a selective dopamine antagonist.

  J Clin Psychopharmacol. 1999 Feb;19(1):45-50

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Management

- Consider it as a possible problem
- Switch to alternative medication (eg. Metoclopramide to domperidone, haloperidol to quertiapine) or reduce dose
- Acute EPS generally resolve with stopping the precipitating drug
- Tardive dyskinesia, dystonia and akathisia can last for years
- Acute treatments may be indicated pending drug clearance:
  - Anti-muscarinic drugs eg. Procyclidine for parkinsonism and dystonia (or benzodiazepine)
  - Akathasia treated by propranolol, antimuscarinic drugs, benzodiazepines or mirtazapine

Summary

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