Psychotropic Medications

Focus on QTc Prolongation

A Sudbury Journal Club Presentation

PRESENTERS

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Disclosure of Commercial Support

THIS PROGRAM HAS RECEIVED FINANCIAL SUPPORT FROM BRISTOL-MYERS SQUIBB CANADA.

THIS PROGRAM HAS RECEIVED IN-KIND SUPPORT FROM BRISTOL-MYERS SQUIBB CANADA IN THE FORM OF LOGISTICAL SUPPORT FOR THE MEETING.

Learning Objectives

- Review of psychotropic medications available in Canada and their indications
- Discuss risks of discontinuation of antipsychotic therapy secondary to adverse events
- Overview and case-based discussion on QTc Prolongation including etiology, risk factors, common drugs, monitoring, and managing risk

Presentation Outline

- Antipsychotic medications available in Canada and their classification
- Review indication, efficacy, and, safety of antipsychotic medication
- QTc prolongation management
- Putting antipsychotic medication risks into perspective
- Potential role of the pharmacist with managing antipsychotic medication use

The Evolution of Therapies…

1940 — ECT

1960-1980 — First Generation APs

- Chlorpromazine
- Trifluoperazine
- Fluphenazine
- Thioridazine
- Haloperidol
- Mesoirdazine
- Loxapine

1990-2000's — Second Generation APs

- Clozapine-2002
- Risperidone-1996
- Olanzapine-1991
- Quetiapine-1998
- Ziprasidone-2004

Last Decade — Second Generation APs

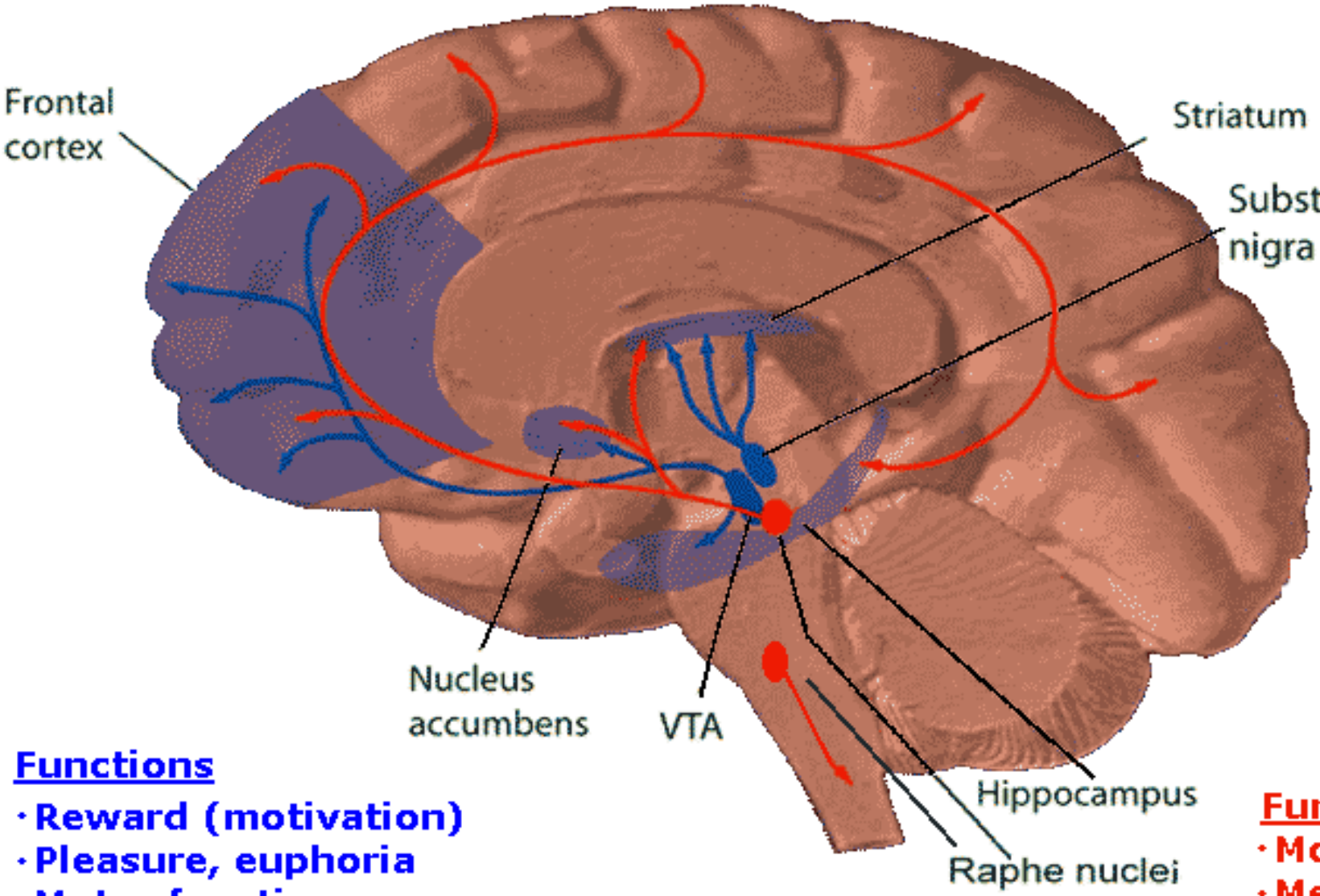
- Aripiprazole-2009
- Asenapine-2012
- Paliperidone-2006
- Lurasidone-2012

Classification of Antipsychotic Therapy

- Conventional/Typical /First Generation
  - Dopaminergic receptors (D2)
  - Not selective: affinity for mesocorticol,nigrostriatal, tuberoinfundibular, and mesolimbic pathways
  - High Potency vs Low Potency
  - Anticholinergic and Antihistaminergic activity
- Atypical/Second Generation
  - Dopaminergic receptors (D2)
  - Affinity for the mesolimbic pathway only
  - Rapid disassociation from dopamine receptors
  - Serotonergic receptors (5HT2A)

Dopamine Pathways

Serotonin Pathways



Functions

- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine tuning)
- Compulsion
- Perseveration

Functions

- Mood
- Memory processing
- Sleep
- Cognition

Table 4. Proposed clinical implications of antipsychotic receptor activities.[13]

Receptor Activity	Possible Clinical Effects
D_2-receptor antagonism	Positive symptom alleviation, EPS, endocrine effects
5-HT_{2A} antagonism	Negative symptom alleviation, less EPS
High 5-HT_{2A}/D_2 binding affinity ratio	Better antipsychotic activity and lower EPS than D_2 antagonism alone
5-HT_{1A} agonism	Antidepressant and anxiolytic activity, improved cognition, reduced EPS, body weight changes
5-HT_{1D} antagonism	Antidepressant activity
5-HT_{2C} antagonism	Positive symptom alleviation, weight gain
α_1-adrenoceptor antagonism	Sedation, hypotension, weight gain
H_1-histamine antagonism	Sedation, weight gain
M_1-muscarinic antagonism	Memory impairment, gastrointestinal symptoms, dry mouth, blurry vision, less EPS
Mixed 5-HT/NE reuptake inhibition	Antidepressant and anxiolytic activity, less weight gain

Casey DE, Zorn SH, The Pharmacology of Weight Gain With Antipsychotics, *The Journal of Clinical Psychiatry,* vol 62, pp 4-10, 2001.

First Generation Antipsychotics Available in Canada

ORAL	Intramuscular Long-Acting
Chlorpromazine (10,25,50,100mg)	Fluanxol Depot (flupentixol) 40mg every 2 weeks
Fluphenazine (1,2,5mg)	Modecate (fluphenazine) 25mg every 2 weeks
Haloperidol (0.5,1,2,5,10,20mg)	Haldol LA 150mg every 4 weeks
Loxapine (2.5,5,10,25,50mg)	Piportil L4 100mg every 4 weeks
Methotrimeprazine (2,5,25,50mg)	Clopixol Depot (zuclopenthixol) 200mg every 2 weeks
Perphenazine (2,4,8,16mg)	
Prochlorperazine (5,10mg)	
Trifluoperazine (1,2,5,10,20mg)	

Second Generation Antipsychotics Available in Canada

ORAL	Intramuscular Long-Acting
Aripiprazole (Abilify) 2,5,10,15,20,30mg	Invega Sustenna (paliperidone) 25-100mg every 4 weeks
Asenapine (Saphris) 5,10mg	Risperdal Consta (risperidone) 25-50mg every 2 weeks
Lurasidone (Latuda) 20,40,60,80,120mg	Abilify Maintena (aripiprazole) 160-400mg every 4 weeks
Olanzapine (Zyprexa) 2.5,5,7.5.10,15,20mg	
Paliperidone (Invega) 3,6,9	
Quetiapine (Seroquel) 25,100,150,200,300mg	
Risperidone (Risperdal) 0.25,0.5,1,2,3,4mg	
Ziprasidone (Zeldox) 20,40,60,80mg	
Iloperidone (Fanapt)-Not approved in CAN	

Patient Profile B.D.

- Medication Profile:
  - Abilify 10mg po daily*
  - Saphris 10mg po bedtime*
  - Lorazepam 2mg po TID
  - Mirtazapine 30mg po bedtime*
  - Pantoprazole 40mg po BID
  - Dicetel 50mg po TID
  - Domperidone 10mg po TID*
  - Trazadone 150mg po bedtime*

Patient Profile T.K.

- Medication Profile:
  - Abilify 5mg po daily*
  - Cipralex 10mg po daily*
  - Synthroid 75mcg po daily
  - Quetiapine XR 250mg po bedtime*
  - Temazepam 30mg po bedtime
  - Trazodone 25mg po bedtime*

How do we determine appropriate pharmacotherapy?

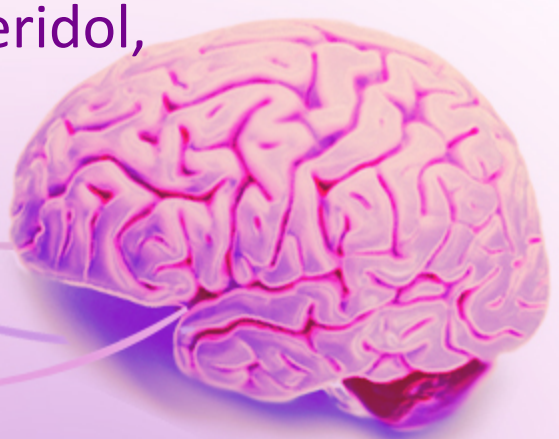
- Presenting Symptoms and Indication
- Proven Efficacy
- Safety
- Past history of response to medications
- Ease of Use/Convenience
- Cost

How do we determine appropriate pharmacotherapy?

- **Presenting Symptoms and Indication**
- Proven Efficacy
- Safety
- Past history of response to medications
- Ease of Use/Convenience
- Cost

Health Canada Approved Indications: First Generation APs

- **Psychosis/Schizophrenia**
- **Nausea/Vomiting**: chlorpromazine, haloperidol, methotrimeprazine, prochlorperazine, trifluoperazine
- **Intermittent porphyria**: chlorpromazine
- **Delirium**: haloperidol
- **Persistent Hiccups**: chlorpromazine and haloperidol
- **Severe agitation/aggression**: haloperidol
- **Behavioural disorder**: chlorpromazine
- **Manic state in bipolar**: chlorpromazine, haloperidol, methotrimeprazine, thioproperazine



Health Canada Approved Indications: Second Generation APs

- **Psychosis/Schizophrenia**
- **Depression**: aripiprazole and quetiapine
- **Manic state in bipolar**: aripiprazole, asenapine, olanzapine, queitapine, riseridone, ziprasidone
- **Depressive state in bipolar**: lurasidone and quetiapine
- **Alzheimer's disease**: risperidone (to control episodes of psychosis with agitation)
- **Behavioural disorder of dementia**: risperidone
- **Generalized anxiety disorder**: risperidone
- **Agitation**: olanzapine

AUTISM SPECTRUM DISORDERS
OBSESSIVE COMPULSIVE DISORDER
INSOMNIA
ANXIETY
AGITATION
DEMENTIA
DELIRIUM
PAIN
DEPRESSION
PTSD
EATING DISORDERS

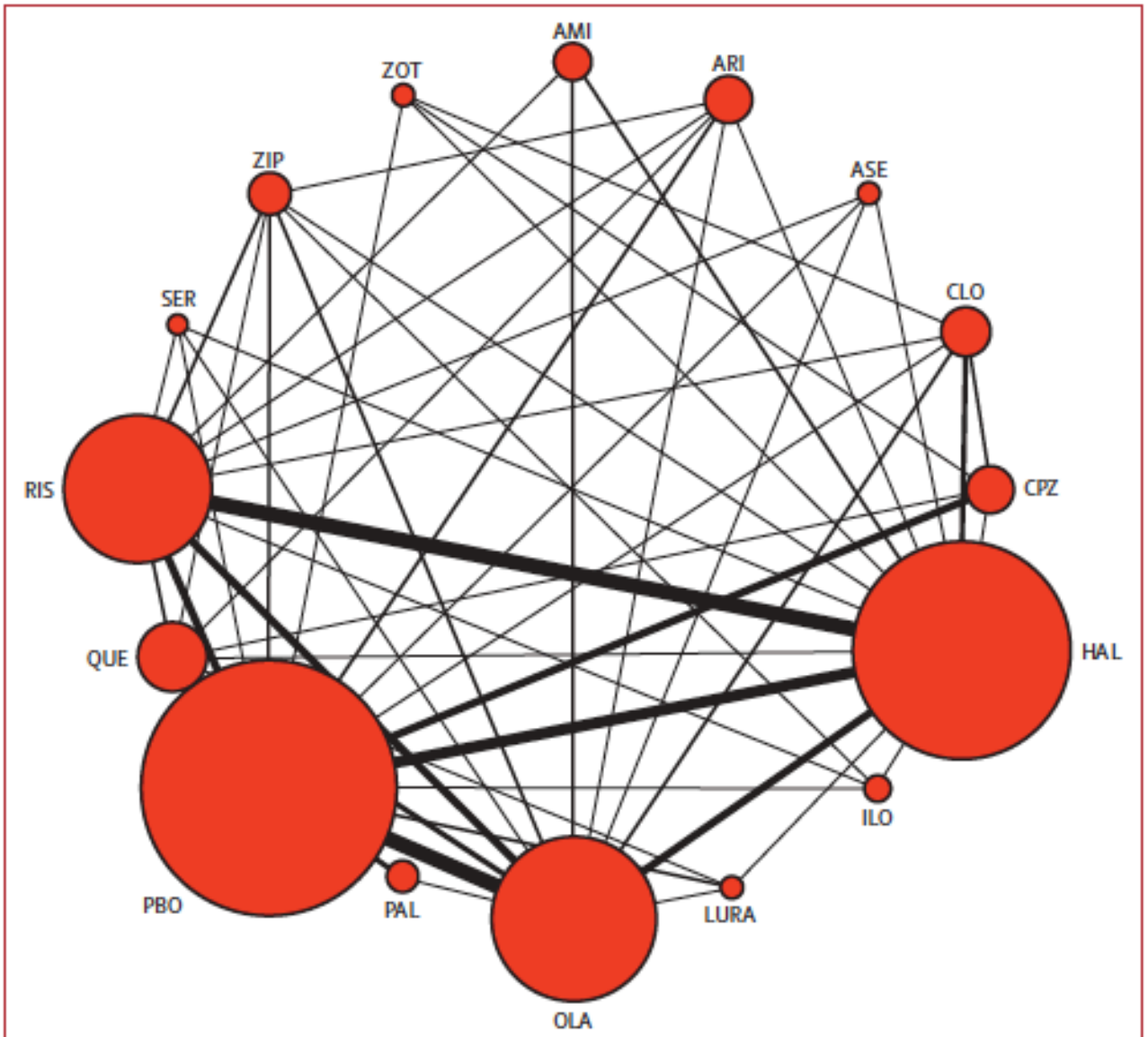
WHAT ABOUT PATIENT'S WITH CO-OCCURRING MENTAL HEALTH DISORDERS?

How do we determine appropriate pharmacotherapy?

- Presenting Symptoms and Indication for Medication Use
- **Efficacy**
- Safety
- Past history of response to medications
- Ease of Use/Convenience
- Cost

Network of Comparative Efficacy

Leucht,S. et al. 2013



CLO	1·10 (0·69 to 1·69)	1·00 (0·68 to 1·43)	0·87 (0·59 to 1·22)	0·97 (0·63 to 1·42)	0·70 (0·39 to 1·16)	0·57 (0·40 to 0·82)	0·76 (0·50 to 1·10)	0·76 (0·51 to 1·09)	0·60 (0·38 to 0·89)	0·65 (0·43 to 0·95)	0·71 (0·48 to 1·01)	0·68 (0·43 to 1·01)	0·61 (0·39 to 0·90)	0·67 (0·45 to 0·99)	0·46 (0·32 to 0·65)
−0·22 (−0·41 to −0·04)	AMI	0·93 (0·69 to 1·22)	0·81 (0·60 to 1·08)	0·90 (0·62 to 1·24)	0·66 (0·37 to 1·10)	0·53 (0·40 to 0·70)	0·70 (0·51 to 0·95)	0·71 (0·51 to 0·96)	0·56 (0·38 to 0·78)	0·60 (0·43 to 0·83)	0·67 (0·44 to 0·95)	0·63 (0·43 to 0·89)	0·56 (0·39 to 0·79)	0·63 (0·44 to 0·87)	0·43 (0·32 to 0·57)
−0·29 (−0·44 to −0·14)	−0·07 (−0·19 to 0·05)	OLA	0·87 (0·76 to 1·01)	0·97 (0·78 to 1·20)	0·71 (0·43 to 1·13)	0·58 (0·50 to 0·66)	0·76 (0·63 to 0·91)	0·76 (0·64 to 0·90)	0·60 (0·47 to 0·76)	0·65 (0·53 to 0·79)	0·72 (0·54 to 0·94)	0·68 (0·53 to 0·86)	0·61 (0·47 to 0·77)	0·68 (0·54 to 0·84)	0·46 (0·41 to 0·52)
−0·32 (−0·47 to −0·16)	−0·09 (−0·21 to 0·03)	−0·03 (−0·10 to 0·04)	RIS	1·12 (0·88 to 1·40)	0·82 (0·49 to 1·29)	0·66 (0·58 to 0·76)	0·87 (0·73 to 1·04)	0·88 (0·72 to 1·06)	0·69 (0·53 to 0·88)	0·75 (0·61 to 0·91)	0·83 (0·61 to 1·08)	0·78 (0·60 to 1·01)	0·70 (0·53 to 0·89)	0·78 (0·62 to 0·96)	0·53 (0·46 to 0·60)
−0·38 (−0·57 to −0·20)	−0·16 (−0·32 to −0·00)	−0·09 (−0·21 to 0·02)	−0·07 (−0·19 to 0·06)	PAL	0·74 (0·43 to 1·20)	0·60 (0·48 to 0·75)	0·79 (0·61 to 1·01)	0·79 (0·61 to 1·02)	0·63 (0·46 to 0·85)	0·68 (0·52 to 0·88)	0·75 (0·53 to 1·02)	0·71 (0·52 to 0·95)	0·63 (0·47 to 0·85)	0·70 (0·53 to 0·93)	0·48 (0·39 to 0·58)
−0·39 (−0·60 to −0·19)	−0·17 (−0·38 to 0·04)	−0·10 (−0·29 to 0·08)	−0·08 (−0·26 to 0·11)	0·01 (−0·22 to 0·20)	ZOT	0·86 (0·51 to 1·32)	1·13 (0·66 to 1·78)	1·14 (0·67 to 1·81)	0·90 (0·51 to 1·46)	0·97 (0·56 to 1·55)	1·07 (0·61 to 1·71)	1·02 (0·58 to 1·65)	0·91 (0·51 to 1·47)	1·01 (0·58 to 1·61)	0·69 (0·41 to 1·07)
−0·43 (−0·58 to −0·28)	−0·21 (−0·32 to −0·09)	−0·14 (−0·21 to −0·08)	−0·11 (−0·18 to −0·05)	−0·05 (−0·16 to 0·08)	−0·04 (−0·21 to 0·14)	HAL	1·32 (1·11 to 1·57)	1·33 (1·11 to 1·57)	1·05 (0·82 to 1·31)	1·13 (0·93 to 1·35)	1·25 (0·93 to 1·63)	1·19 (0·92 to 1·50)	1·06 (0·82 to 1·34)	1·17 (0·95 to 1·43)	0·80 (0·71 to 0·90)
−0·44 (−0·61 to −0·28)	−0·22 (−0·36 to −0·08)	−0·15 (−0·25 to −0·06)	−0·13 (−0·22 to −0·03)	−0·06 (−0·19 to 0·08)	−0·05 (−0·24 to 0·14)	−0·01 (−0·10 to 0·08)	QUE	1·01 (0·80 to 1·25)	0·80 (0·60 to 1·04)	0·86 (0·68 to 1·07)	0·95 (0·69 to 1·26)	0·90 (0·68 to 1·19)	0·81 (0·61 to 1·03)	0·89 (0·70 to 1·13)	0·61 (0·52 to 0·71)
−0·45 (−0·62 to −0·28)	−0·23 (−0·37 to −0·08)	−0·16 (−0·25 to −0·07)	−0·13 (−0·23 to −0·03)	−0·07 (−0·20 to 0·08)	−0·06 (−0·25 to 0·14)	−0·02 (−0·12 to 0·08)	−0·01 (−0·12 to 0·11)	ARI	0·80 (0·59 to 1·04)	0·86 (0·68 to 1·07)	0·95 (0·69 to 1·27)	0·90 (0·68 to 1·18)	0·80 (0·6 to 1·05)	0·89 (0·69 to 1·14)	0·61 (0·51 to 0·72)
−0·49 (−0·68 to −0·30)	−0·27 (−0·43 to −0·10)	−0·20 (−0·33 to −0·06)	−0·17 (−0·31 to −0·04)	−0·10 (−0·27 to 0·07)	−0·09 (−0·31 to 0·12)	−0·06 (−0·19 to 0·07)	−0·04 (−0·19 to 0·10)	−0·04 (−0·19 to 0·11)	SER	1·09 (0·81 to 1·45)	1·21 (0·84 to 1·69)	1·14 (0·81 to 1·56)	1·02 (0·73 to 1·39)	1·13 (0·83 to 1·52)	0·78 (0·61 to 0·98)
−0·49 (−0·66 to −0·31)	−0·26 (−0·41 to −0·12)	−0·20 (−0·29 to −0·10)	−0·17 (−0·27 to 0·07)	−0·10 (−0·24 to 0·04)	−0·09 (−0·29 to 0·11)	−0·05 (−0·15 to 0·04)	−0·04 (−0·16 to 0·08)	−0·04 (−0·16 to 0·09)	0·00 (−0·15 to 0·16)	ZIP	1·11 (0·80 to 1·50)	1·06 (0·78 to 1·41)	0·94 (0·70 to 1·24)	1·05 (0·81 to 1·33)	0·72 (0·59 to 0·86)
−0·50 (−0·67 to −0·33)	−0·27 (−0·47 to −0·08)	−0·21 (−0·37 to −0·05)	−0·18 (−0·34 to −0·02)	−0·11 (−0·30 to 0·08)	−0·10 (−0·32 to 0·11)	−0·07 (−0·22 to 0·09)	−0·05 (−0·22 to 0·11)	−0·05 (−0·22 to 0·13)	−0·01 (−0·21 to 0·19)	−0·01 (−0·19 to 0·16)	CPZ	0·96 (0·66 to 1·34)	0·86 (0·61 to 1·19)	0·96 (0·68 to 1·32)	0·65 (0·50 to 0·84)
−0·50 (−0·69 to −0·30)	−0·27 (−0·45 to −0·10)	−0·21 (−0·34 to −0·08)	−0·18 (−0·32 to −0·04)	−0·11 (−0·28 to 0·05)	−0·10 (−0·32 to 0·11)	−0·07 (−0·20 to 0·07)	−0·05 (−0·20 to 0·09)	−0·05 (−0·20 to 0·10)	−0·01 (−0·19 to 0·17)	−0·01 (−0·17 to 0·14)	0·00 (−0·20 to 0·20)	ASE	0·91 (0·64 to 1·22)	1·01 (0·73 to 1·36)	0·69 (0·54 to 0·86)
−0·55 (−0·74 to −0·36)	−0·33 (−0·50 to −0·16)	−0·26 (−0·39 to −0·13)	−0·23 (−0·37 to −0·10)	−0·17 (−0·33 to −0·00)	−0·16 (−0·37 to 0·06)	−0·12 (−0·25 to 0·01)	−0·11 (−0·25 to 0·03)	−0·10 (−0·25 to 0·05)	−0·06 (−0·24 to 0·11)	−0·07 (−0·22 to 0·09)	−0·05 (−0·25 to 0·14)	−0·05 (−0·23 to 0·12)	LUR	1·12 (0·83 to 1·50)	0·77 (0·61 to 0·96)
−0·55 (−0·73 to −0·38)	−0·33 (−0·48 to −0·18)	−0·26 (−0·38 to −0·15)	−0·24 (−0·35 to −0·12)	−0·17 (−0·32 to −0·02)	−0·16 (−0·36 to 0·04)	−0·12 (−0·23 to −0·02)	−0·11 (−0·24 to 0·02)	−0·10 (−0·24 to 0·03)	−0·07 (−0·23 to 0·10)	−0·07 (−0·20 to 0·06)	−0·06 (−0·24 to 0·13)	−0·06 (−0·22 to 0·11)	0·00 (−0·16 to 0·16)	ILO	0·69 (0·56 to 0·84)
−0·88 (−1·03 to −0·73)	−0·66 (−0·78 to −0·53)	−0·59 (−0·65 to −0·53)	−0·56 (−0·63 to −0·50)	−0·50 (−0·60 to −0·39)	−0·49 (−0·66 to −0·31)	−0·45 (−0·51 to −0·39)	−0·44 (−0·52 to −0·35)	−0·43 (−0·52 to −0·34)	−0·39 (−0·52 to −0·26)	−0·39 (−0·49 to −0·30)	−0·38 (−0·54 to −0·23)	−0·38 (−0·51 to −0·25)	−0·33 (−0·45 to −0·21)	−0·33 (−0·43 to −0·22)	PBO

Treatment Efficacy (SMD with 95% CrI) All cause discontinuation (OR with 95% CrI)

Are SGAs more effective than FGAs?

- Two important clinical trials that shed light on this controversy:
  - Clinical Antipsychotic Trials of Effectiveness (NIMH)
  - Cost Utility of the Latest Antipsychotics in severe schizophrenia (NHS)

- Two take home points:
  - No evidence of benefit of SGAs over FGAs for the treatment of negative symptoms of schizophrenia
  - Clozapine has shown clear utility in treatment-resistant cases of schizophrenia

Table A. Summary of strength of evidence of efficacy, by drug and condition

		Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Anxiety	generalized anxiety disorder	O	-	++	-	-
	social phobia	O	+	-	O	O
Attention Deficit/Hyperactivity Disorder	no co-occurring disorders	O	O	O	+	O
	bipolar children	-	O	O	O	O
	mentally retarded children	O	O	O	+	O
Dementia	overall	++	+	+	++	O
	psychosis	+	+-	+-	++	O
	agitation	+	++	+-	++	O
Depression	MDD augmentation of SSRI/SNRI	++	+	++	++	+
	MDD: Monotherapy	O	-	++	O	O
Eating Disorders		O	—	-	O	O
Insomnia		O	O	-	O	O
Obsessive Compulsive Disorder	augmentation of SSRI	O	+	—	++	-
	augmentation of citalopram	O	O	+	+	O
Personality Disorder	borderline	+	+-	+	O	-
	schizotypal	O	O	O	+-	O
Post Traumatic Stress Disorder		O	+-	+	++	O
Substance Abuse	alcohol	—	-	-	O	O
	cocaine	O	-	O	-	O
	methamphetamine	-	O	O	O	O
	methadone clients	O	O	O	-	O
Tourette's Syndrome		O	O	O	+	-

++	moderate or high evidence of efficacy
+	low or very low evidence of efficacy
+-	mixed results
-	low or very low evidence of inefficacy
—	moderate or high evidence of inefficacy
O	no trials

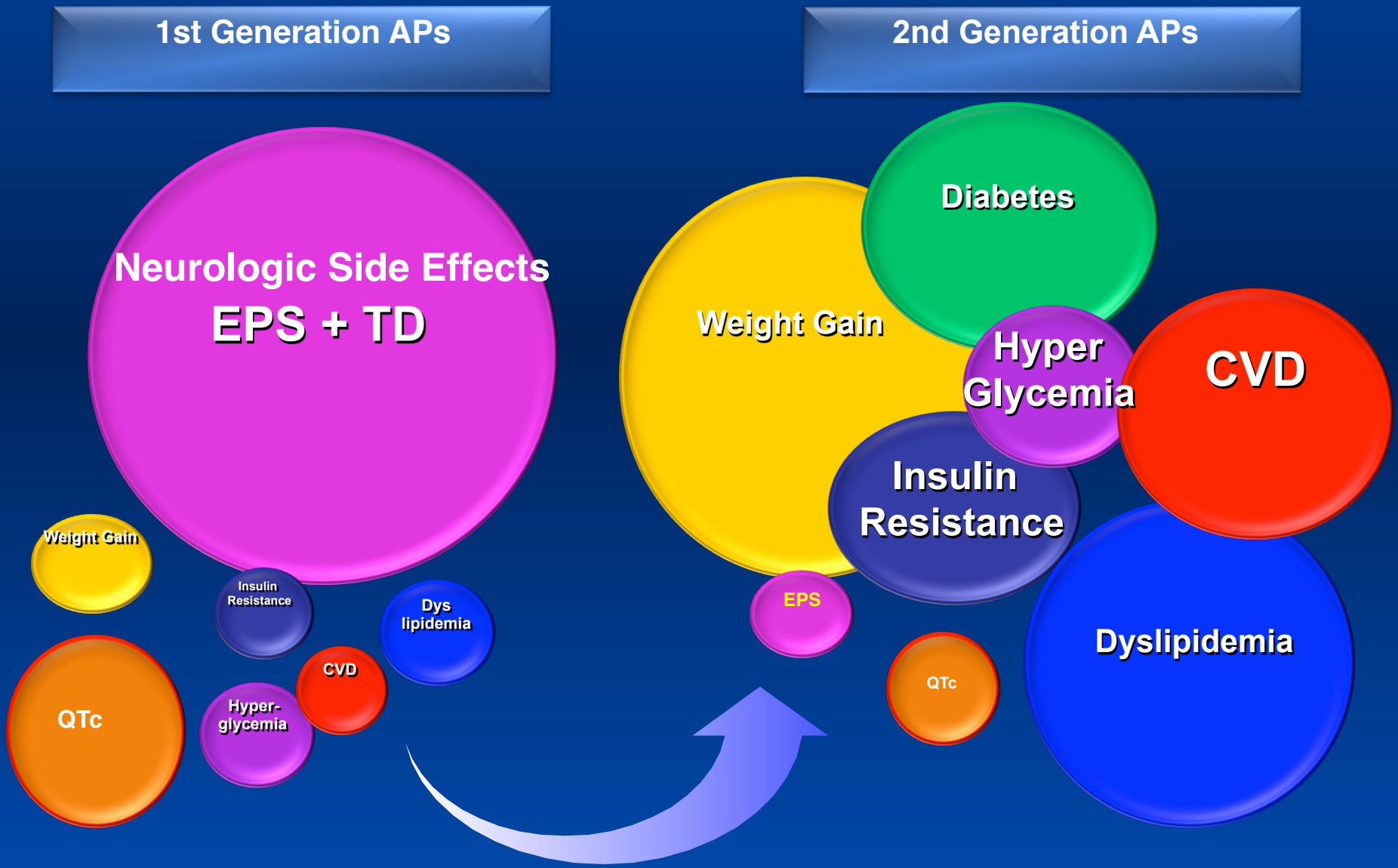
AHRQ Pub. No. 11-EHC087-1
September 2011

THE WIDE ARRAY OF DRUG THERAPIES NOW AVAILABLE ALLOW CLINICIANS TO TAILOR TREATMENT TO EACH INDIVIDUAL'S NEEDS AND PREFERENCES, ENHANCING ACCEPTABILITY AND LONG-TERM ADHERENCE.

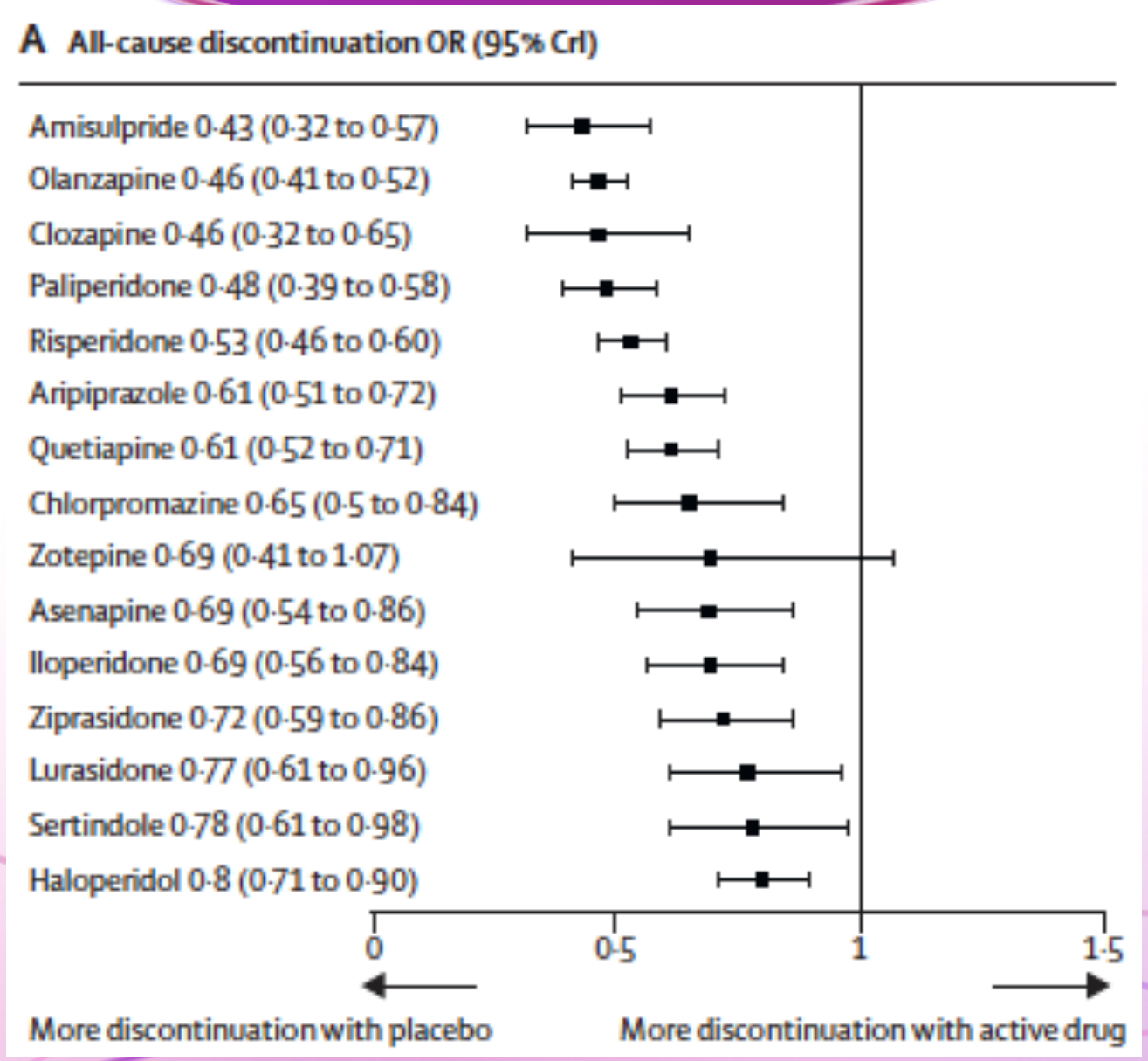
How do we determine appropriate pharmacotherapy?

- Presenting Symptoms and Indication for Medication Use
- Proven Efficacy
- **Safety**
- Past history of response to medications
- Ease of Use/Convenience
- Cost

Side Effects Profile of Antipsychotics



Side Effect Hierarchies for Psychosis/Schizophrenia



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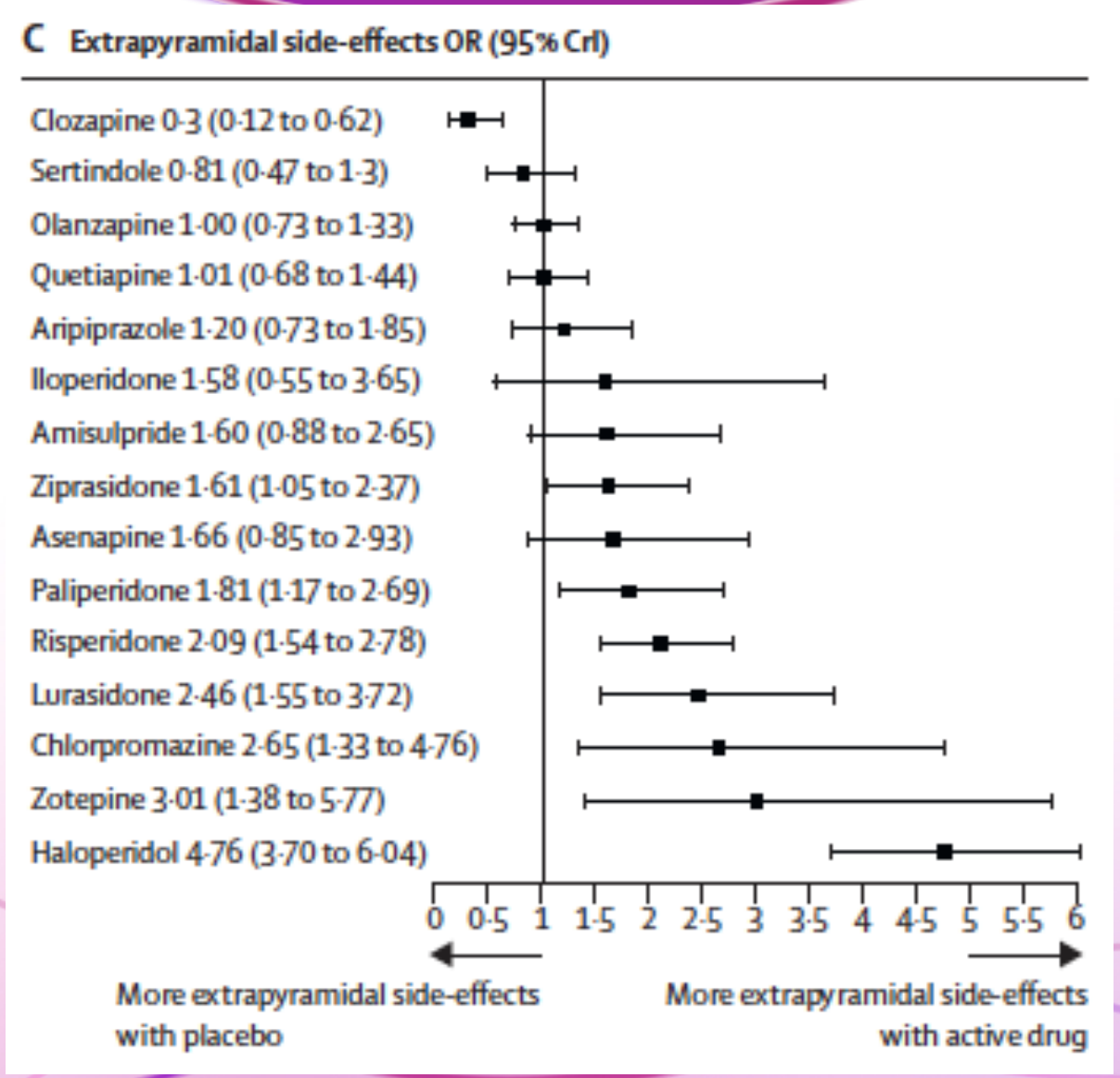
Side Effect Hierarchies for Psychosis/Schizophrenia



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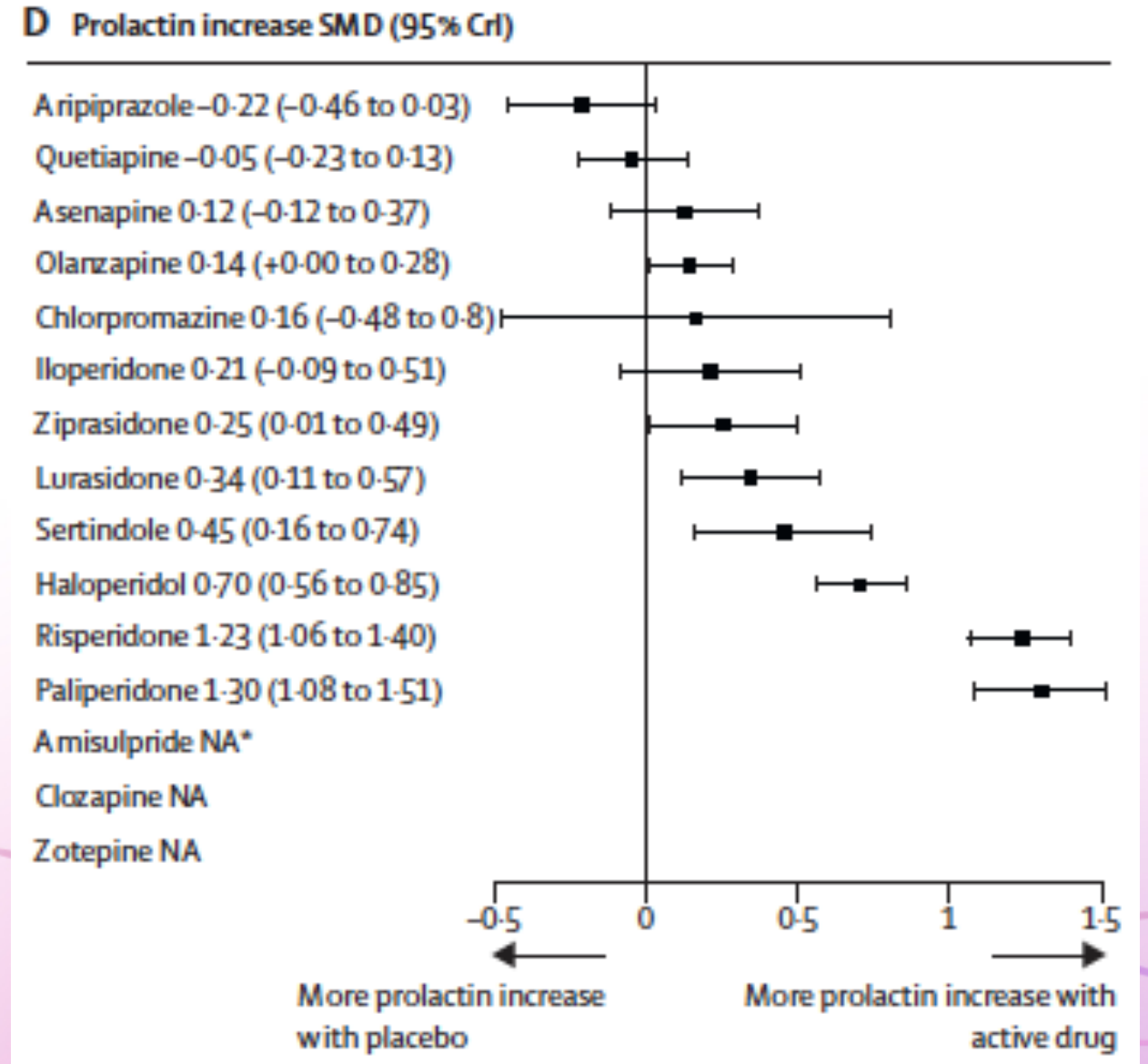
Side Effect Hierarchies for Psychosis/Schizophrenia



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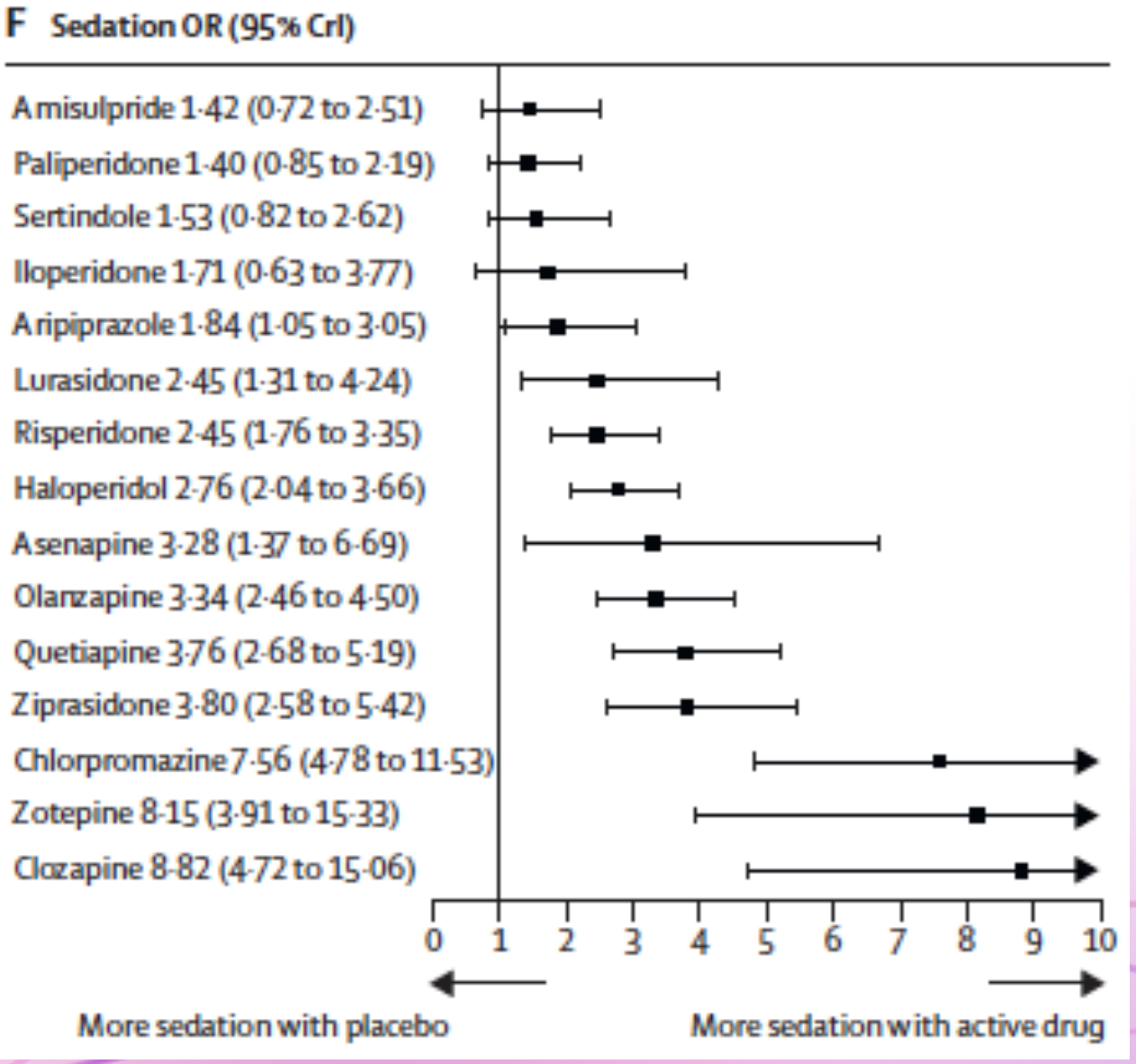
Side Effect Hierarchies for Psychosis/Schizophrenia



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Quit Playing Games With My Heart!

QTc Prolongation

QTc Prolongation Outline

- Case
- Etiology
- Risk factors
- Common drugs
- Antipsychotics and QTc Prolongation
- Challenges in Community Pharmacy
- Managing risk
- Systematic Approach to managing QTc Prolongation
- Summary

Remember this?

Subject: Domperidone associated with serious abnormal heart rhythms and sudden death (cardiac arrest)

Some patients taking domperidone may have a small increased risk of serious abnormal heart rhythms or sudden cardiac arrest if they:

- **use doses higher than 30 mg a day;**
- **are older than 60 years of age;**
- **have certain conditions or take other drugs that may change the electrical activity of the heart (QT prolongation).**

http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2015/43423a-eng.php

Myth Buster!

- The warning was based on 2 CASE CONTROLLED studies which used data retrieved from electronic databases.
- Limitations: researchers were only able to examine if a Rx for domperidone was filled. Whether or not the individual took the medication was not confirmed.

Bozzo P, Koren G, Ito S. Health Canada advisory on domperidone should I avoid prescribing domperidone to women to increase milk production [corrected]?. Can Fam Physician. 2012;58(9):952-3.

Myth Buster!

- In the study conducted in the Netherlands, domperidone is available OTC; therefore, all exposures to domperidone were not captured.
- Studies lacked data on specific triggers of drug induced TdP such as digitalis toxicity, hypokalemia, hyperkalemia or hypomagnesemia
- **Overall risk of sudden cardiac death was 7 in 10,000**

Bozzo P, Koren G, Ito S. Health Canada advisory on domperidone should I avoid prescribing domperidone to women to increase milk production [corrected]?. Can Fam Physician. 2012;58(9):952-3.

Now That I Have Your Attention!

Case: Meet the Patient

Name: Mrs. Bee
Age/Sex: 70 y.o female
Past Medical History:

- Schizoaffective disorder & comorbid anxiety disorder (40 year hx)
- Type 2 diabetes mellitus
- Hypertension

Case: Meet the Patient

Social History:

- *Mrs. Bee's husband died 5 years ago*
- *She lives alone in a senior care facility*
- *Uses a weekly pill reminder box that she fills herself because her residential facility does not monitor medication adherence*
- *Sees her psychiatrist once a month and her primary care provider every 3 months*
- *No history of illicit drug, alcohol, or tobacco use*

Case: Mrs. Bee's Medications

- Furosemide 40mg PO once daily (hypertension)
- Lisinopril 20 mg PO once daily (hypertension)
- Metformin 1500 mg PO once daily (T2DM)
- Lorazepam 1.5 mg PO once daily (anxiety)
- Paroxetine 40 mg PO once daily (anxiety)
- Quetiapine 800 mg PO once daily (*psychotic features and mood de-regulation with schizoaffective disorder)*

She Presents with a prescription from a walk-in clinic for Azithromycin 500 mg on day 1 followed by 250 mg once daily on days 2-5.

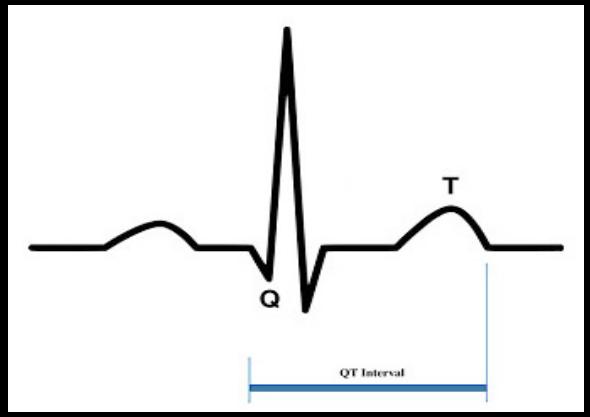
Case: To be continued…

- Keep Mrs. Bee in Mind, we will be re-visiting her again shortly….

What is QTc Prolongation?

- An inherited or acquired disturbance of the heart's electrical system caused by abnormalities of ion channels found in heart cells.

- Ions (K^+, Na^+, Ca^{2+} and Cl^-) pass across the cell membrane through channels and generate the electrical activity (depolarization and repolarization) that initiates the heart's mechanical function.



What is QTc Prolongation?

- These electrical signals are recorded as the electrocardiogram (EKG or ECG).
- The abnormal function of one or more ion channels prolongs the repolarization process and the QT interval. This predisposes patients to cardiac arrhythmias.

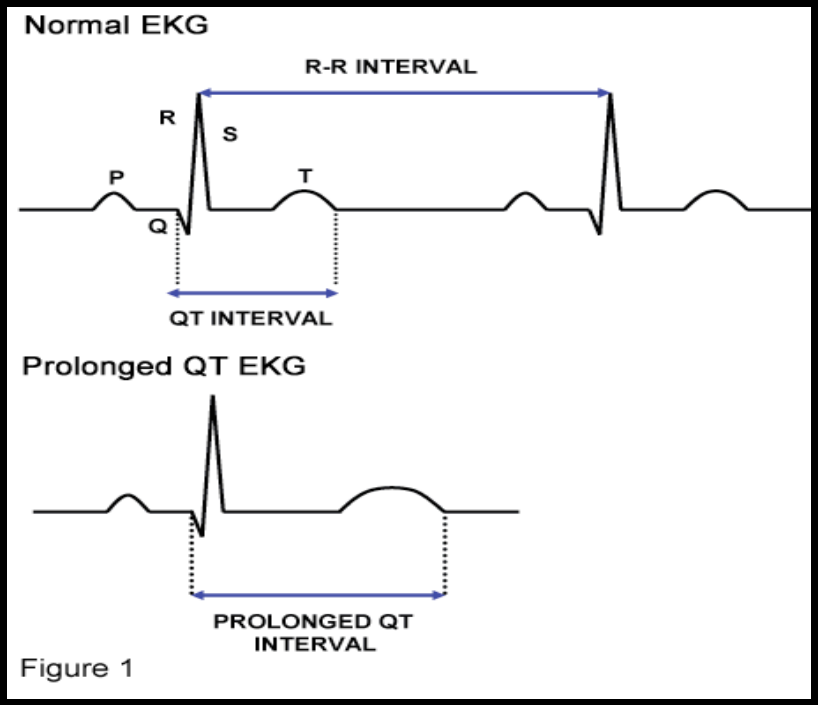
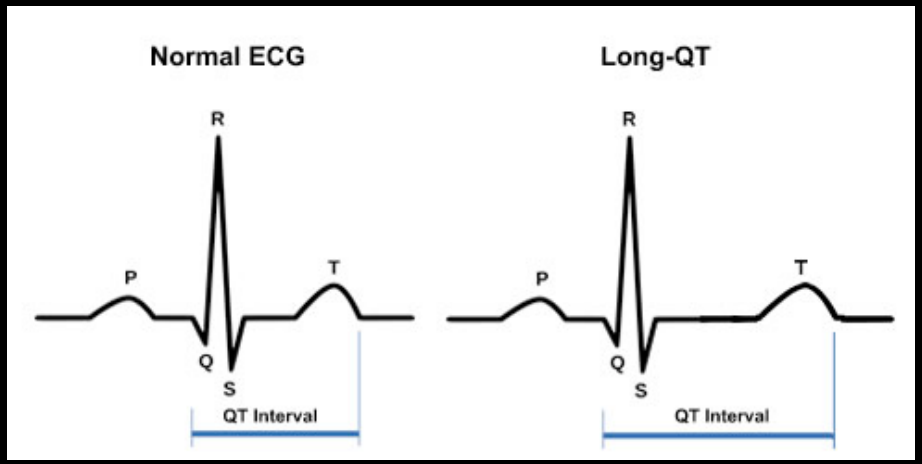


Figure 1

What is the QTc Interval?

- The time from the electrical stimulation (depolarization) of the heart's pumping chambers (ventricles), to their recharging (repolarization).
- The QT interval varies with heart rate. It shortens as the rate increases and lengthens as the rate decreases.
- Therefore, there is no single QT interval that is normal or abnormal.



Range of QTc Intervals

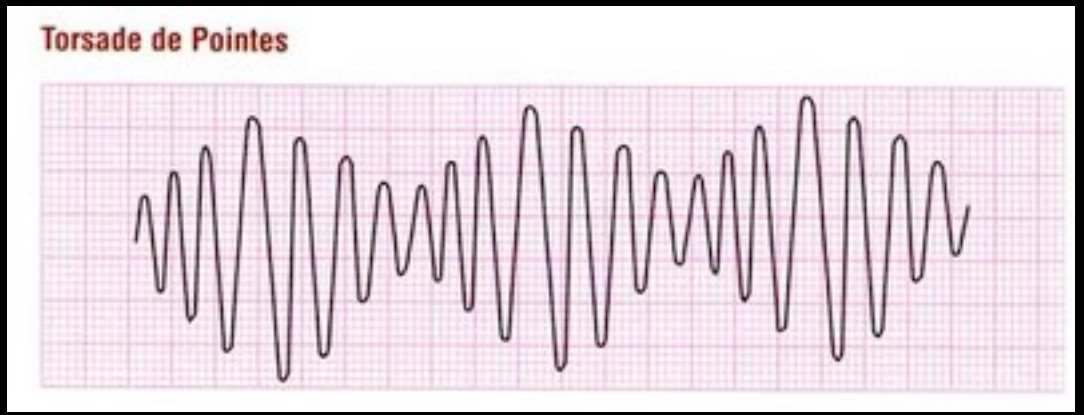
In order to determine if a given QT is appropriate for a given heart rate, the QT is corrected for the heart rate using a mathematical formula, and this quantity is called the QTc.

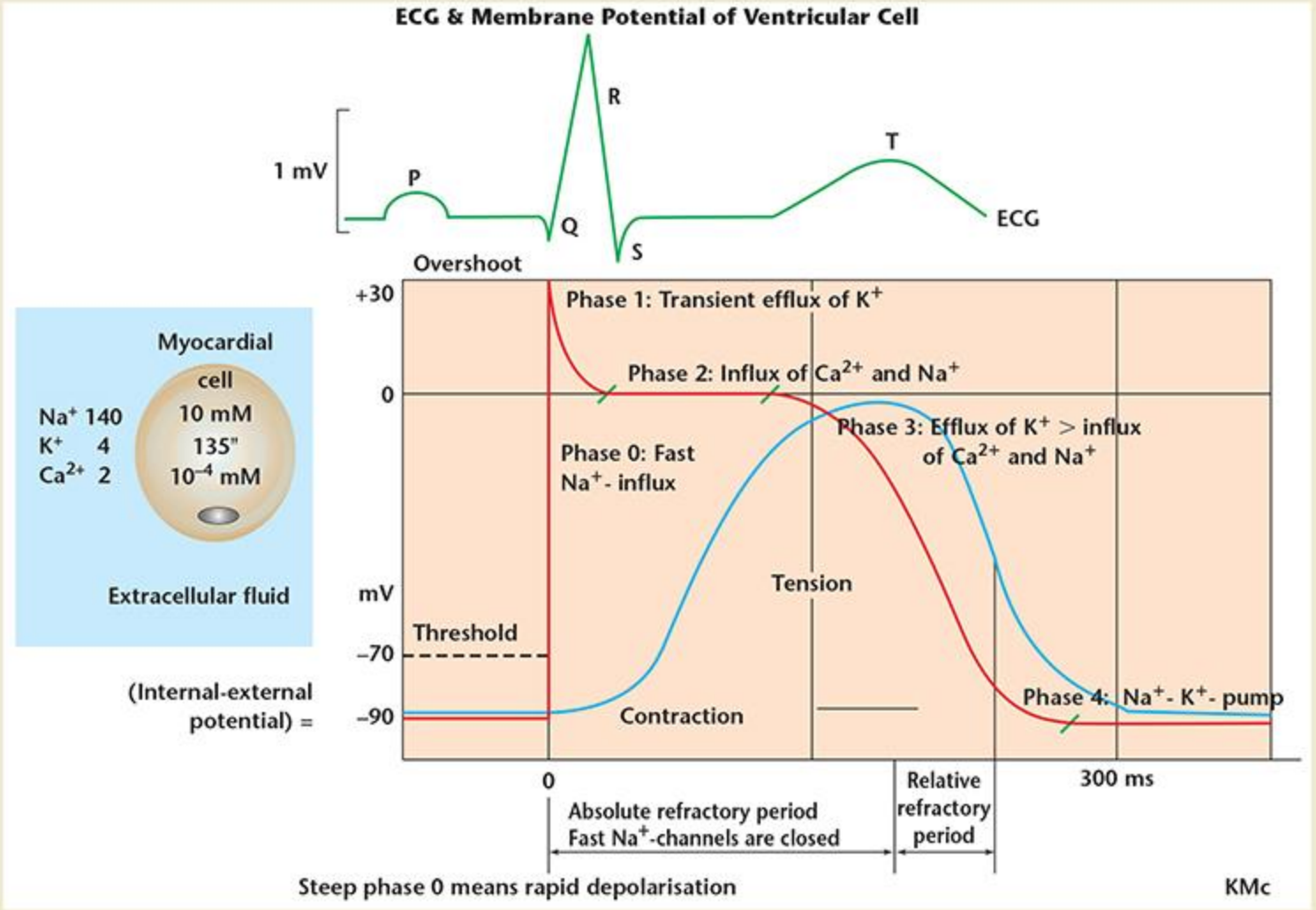
	Males	Females
Normal	Less than 430 msec	Less than 450 msec
Borderline	430-450 msec	450-470 msec
Prolonged	Greater than 450 msec	Greater than 470 msec

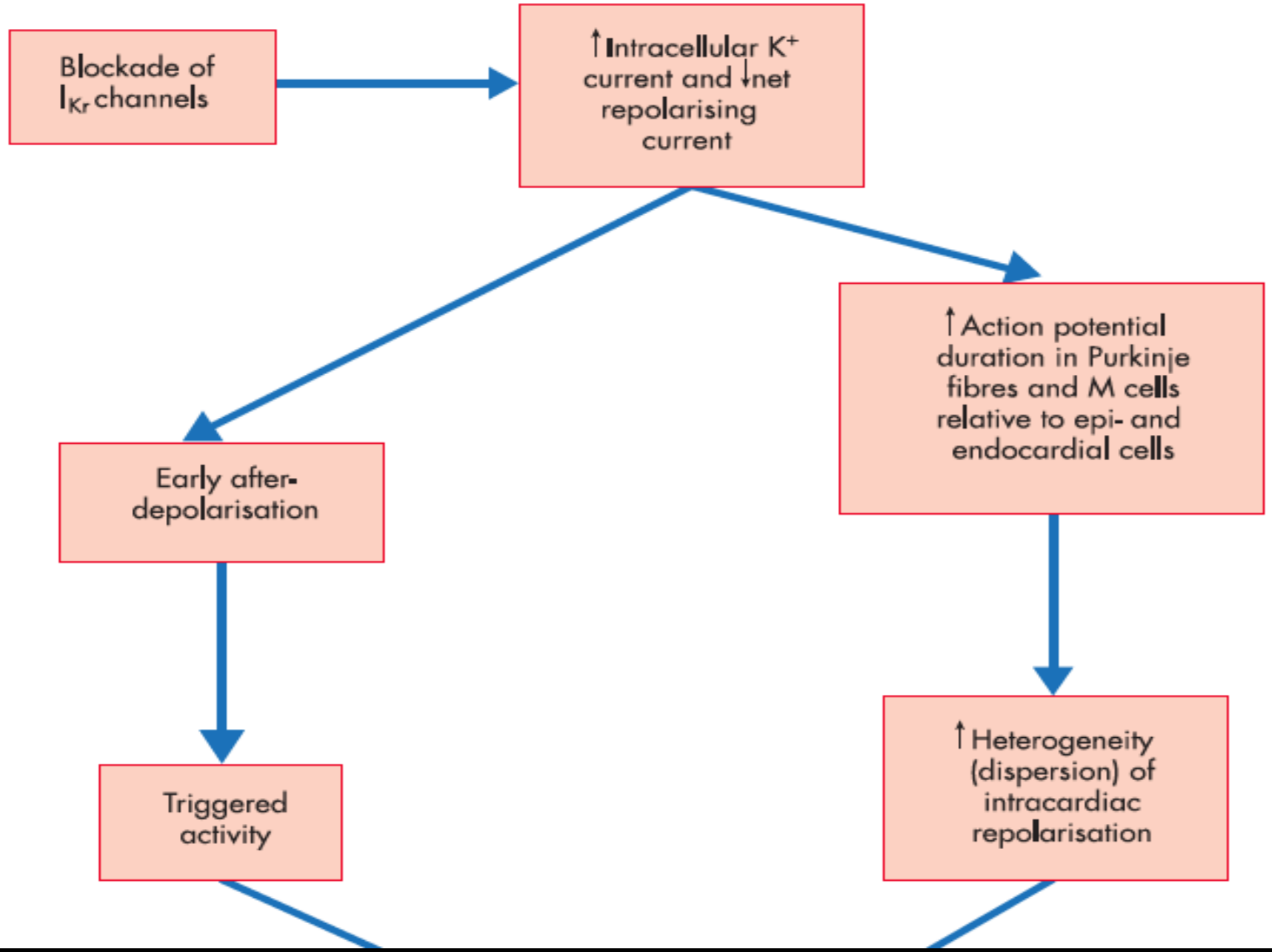
Why are we concerned..?

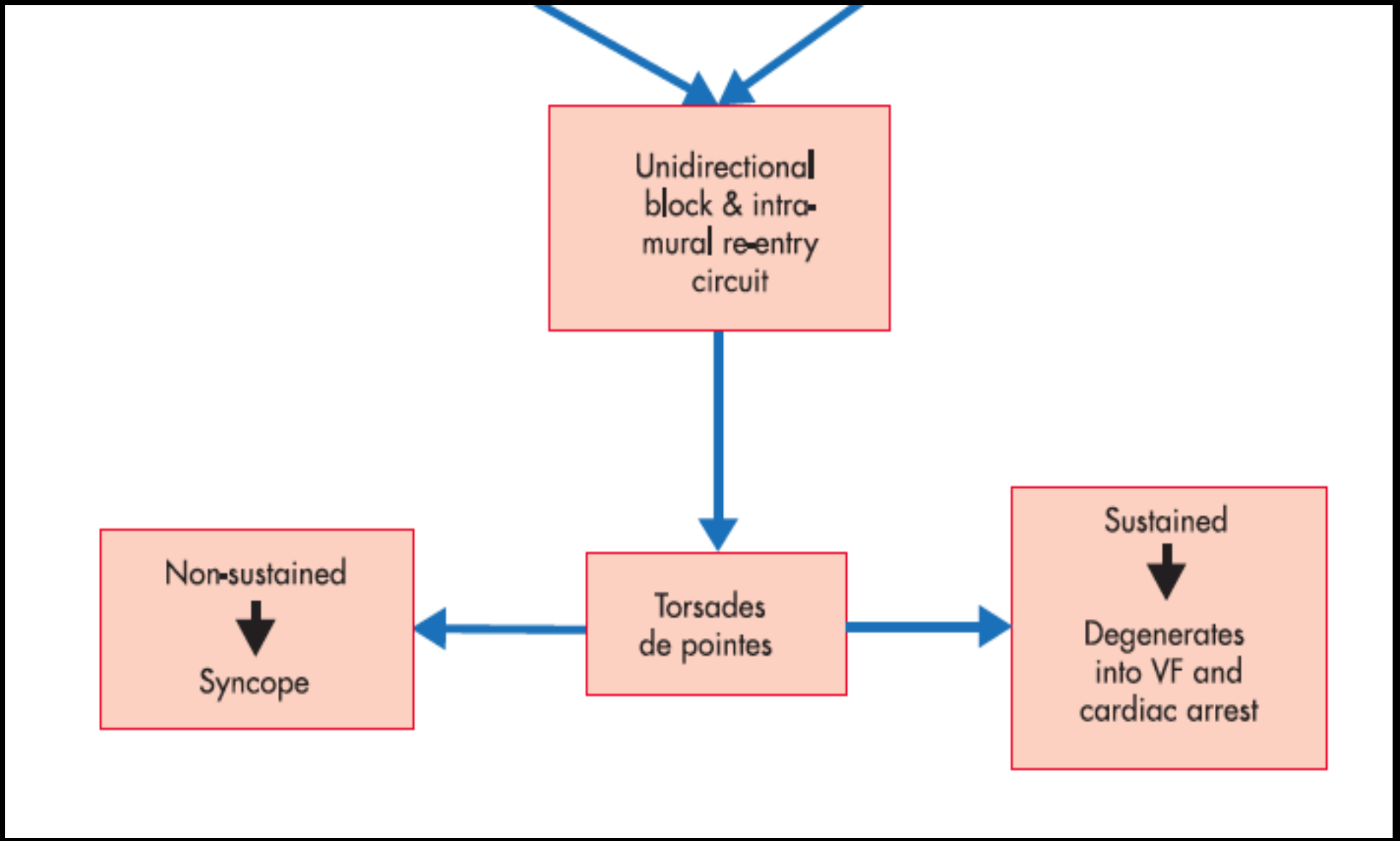
Torsades de Pointes(TdP)

- TdP (twisting of the points) refers to a polymorphic ventricular tachycardia, associated with prolonged QTc interval and bradycardia.
- TdP is thought to be caused by early after-depolarizations during prolonged repolarization. It is often self-limiting but may be **potentially fatal**, sometimes leading to syncope and/or sudden death.
- TdP can be either 1° (congenital) or 2° (acquired) due to metabolic disturbances, medical conditions, or **most commonly**, drugs
- The actual incidence of TdP is unknown.
- Numerous drugs have the potential to cause TdP and have been taken off the market for that reason!




ECG & Membrane Potential of Ventricular Cell
1 mV
P
R
Q
S
T
ECG
Overshoot
+30
0
mV
–70
–90
Phase 1: Transient efflux of K+
Phase 2: Influx of Ca2+ and Na+
Phase 3: Efflux of K+ > influx of Ca2+ and Na+
Phase 0: Fast Na+- influx
Tension
Threshold
Contraction
Phase 4: Na+- K+- pump
Myocardial cell
Na+ 140
K+ 4
Ca2+ 2
10 mM
135"
10–4 mM
Extracellular fluid
(Internal-external potential) =
0
300 ms
Relative refractory period
Absolute refractory period
Fast Na+-channels are closed
Steep phase 0 means rapid depolarisation
KMc


Blockade of I_{Kr} channels
↑Intracellular K^+ current and ↓net repolarising current
Early after-depolarisation
↑Action potential duration in Purkinje fibres and M cells relative to epi- and endocardial cells
Triggered activity
↑Heterogeneity (dispersion) of intracardiac repolarisation


Unidirectional block & intra-mural re-entry circuit
Non-sustained
Syncope
Torsades de pointes
Sustained
Degenerates into VF and cardiac arrest

Why do we care about other risk factors?

- It is important to keep in mind that the QT interval is simply a surrogate marker for the risk of TdP.

- The risk of TdP does not directly correlate with the QT interval or the extent of QT-interval prolongation.

Risk Factors

Disease States or Nonmodifiable Risk Factors	Modifiable Risk Factors
Cardiovascular disease (including previous left ventricular hypertrophy, heart failure, coronary artery disease and bradyarrhythmias)	Electrolyte disturbances (hypokalemia, hypomagnesemia, hypocalcemia)
Eating disorders (which may predispose a person to having electrolyte disturbances)	Use of more than one QT-prolonging medication (e.g., antiarrhythmics, some antipsychotics, gastric motility agents, and certain macrolide and quinolone antibiotics)
Female sex	
Increasing age	Use of a medication that increases the blood concentration of a QT-prolonging medication (e.g., omeprazole reducing the metabolism of citalopram) or causes an electrolyte disturbance
Liver or kidney impairment (which may reduce the metabolism of a QT-prolonging medications)	

Table 1: Nonmodifiable and modifiable risk factors in developing TdP

Gören JL, Dinh TA. Psychotropics and sudden cardiac death. R I Med J (2013); 96(3):38-41.

Remember Mrs Bee?!

- What were some of her Risk Factors?

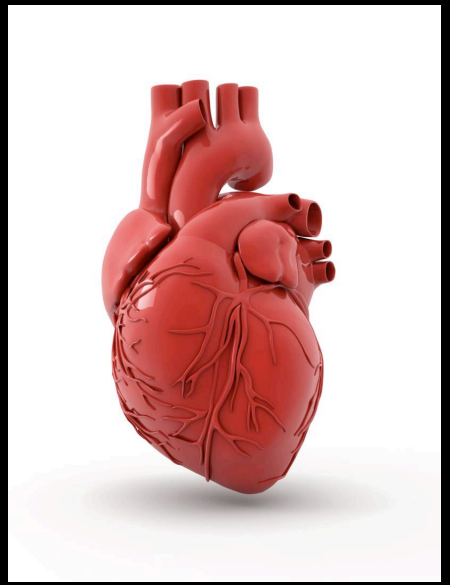
Mrs. Bee's Risk Factors

- Non-Modifiable:
  - -Female sex
  - -Increased age
- Modifiable:
  - -Potential electrolyte disturbances due to furosemide
  - -Use of more than one QT prolonging medication (Quetiapine and Paroxetine)

Stratification of Risk Factors

Highest Risk (Risk factors in no particular order):

- Age: Increased risk with increased age
- Female Sex: longer baseline QT intervals than men
- Cardiomyopathy: Heart failure, Left Ventricular hypertrophy, Myocardial Infarction
- Congenital Long QT Interval: Rare (incidence 1/5000)
- Drugs

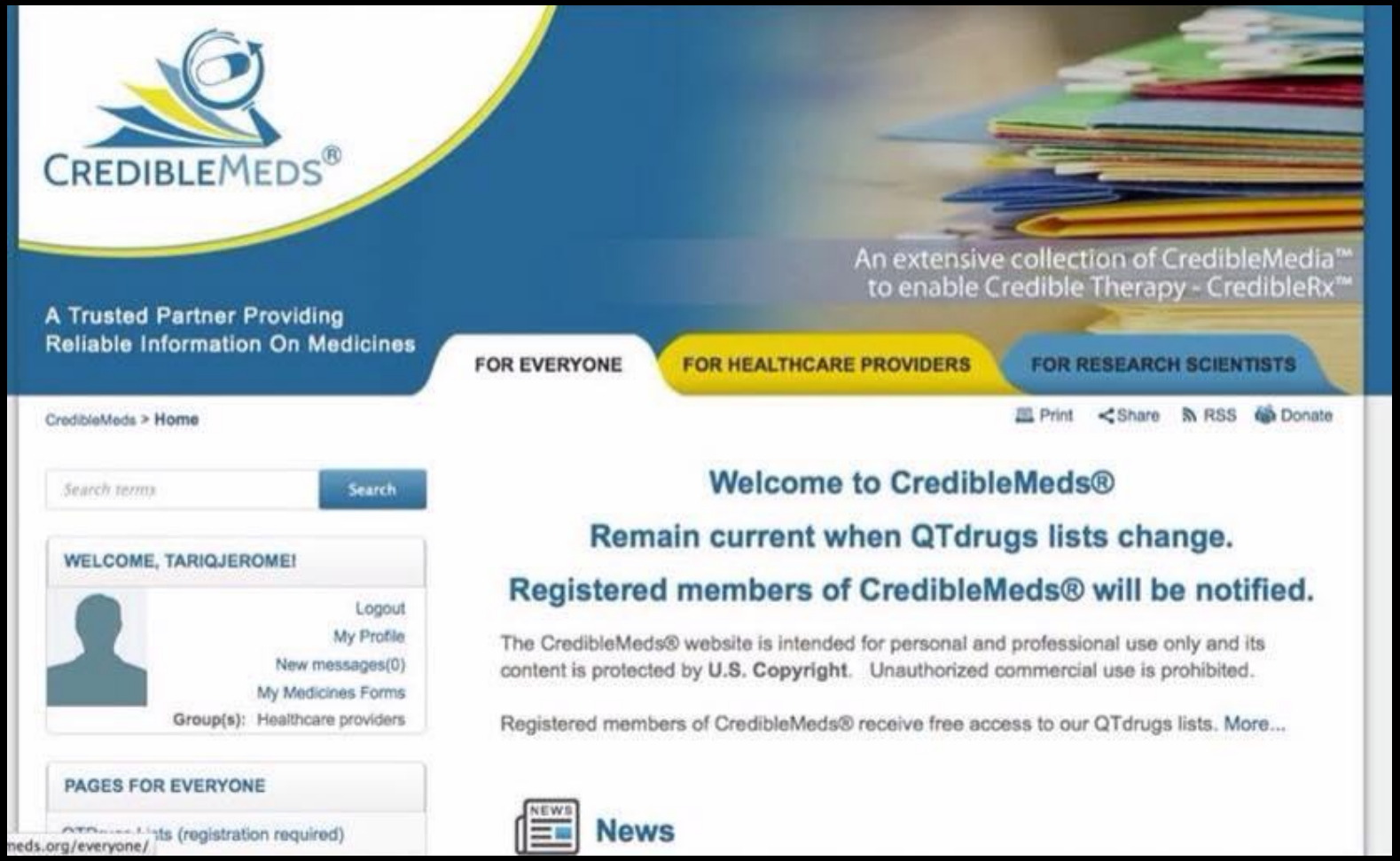


Drugs

- More than 50 commonly prescribed medications can lead to drug-induced QT prolongation…
- With so many drugs that can cause QT prolongation how do we go about stratifying risk of potential drug-induced QT prolongation?

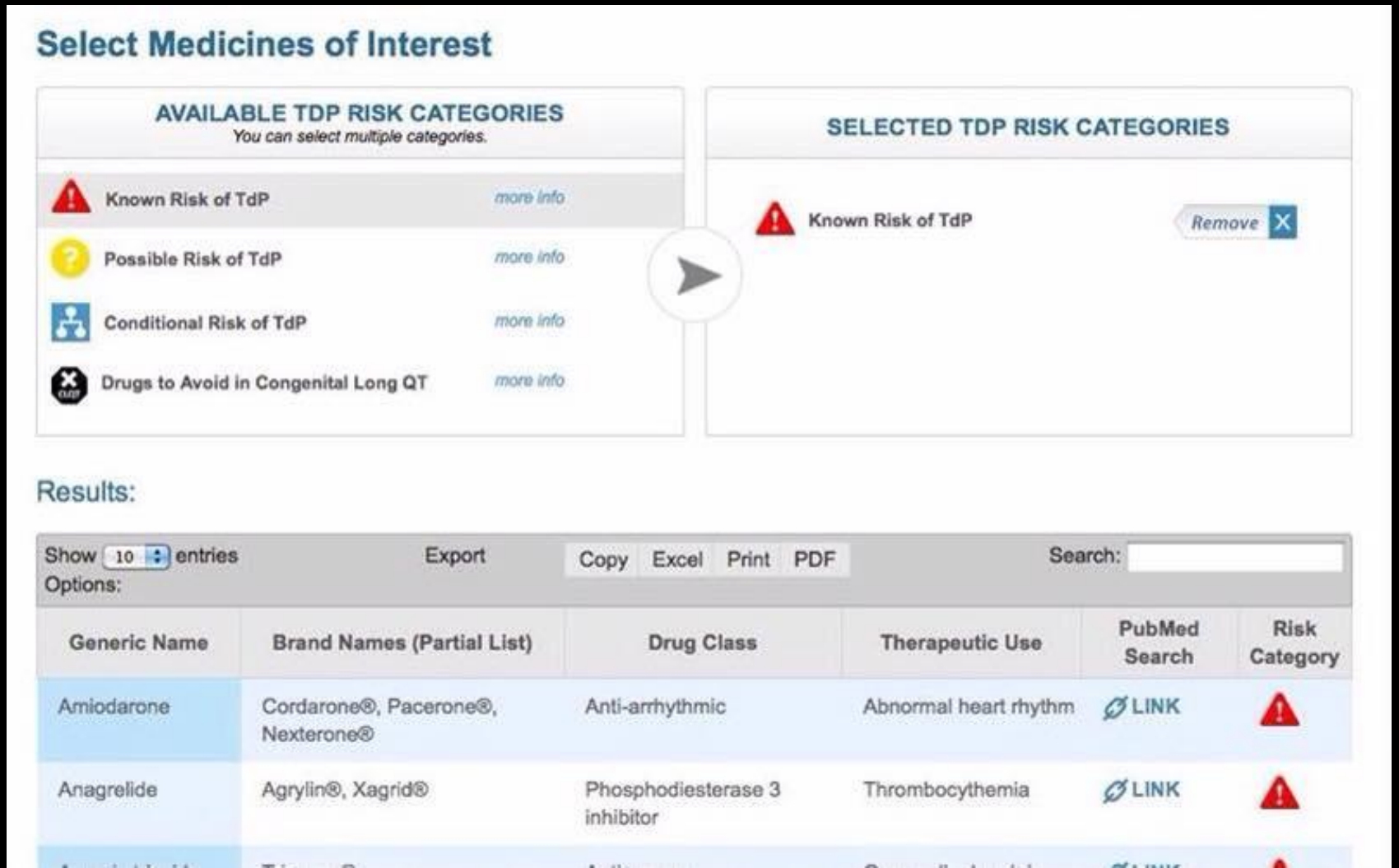
Stratification of Risk Factors

- Credible Meds → Free Resource!



Stratification of Risk Factors

- Credible Meds → Free Resource!



High Risk QT Prolonging Medications

High Risk Medications	
Antiarrhythmics: • amiodarone • disopyramide • dofetilide • ibutilide • procainamide • quinidine • sotalol	*Miscellaneous:* • arsenic • cisapride • droperidol • thioridazine • pentamidine

Table 2: High risk QTc prolonging medications

2007. University of Illinois College of Pharmacy**Drug-induced QT prolongation (Part 2): a focus on select medications**.http://dig.pharm.uic.edu/faq/2013/Feb/faq2.aspx

Medium Risk QT Prolonging Medications

Medium Risk Medications

Psychotropics:

Phenothiazines:
- chlorpromazine
- fluphenazine
- mesoridazine
- perphenazine
- trifluoperazine

Atypicals
- clozapine
- paliperidone
- quetiapine
- risperidone
- ziprasidone

Others:
- haloperidol
- venlafaxine
- pimozide

Antimicrobials:

Quinolones (ranked from highest to lowest risk)
- moxifloxacin
- levofloxacin
- ofloxacin

Azoles:
- voriconazole

Antimalarials:
- chloroquine
- halofantrine
- mefloquine

Macrolides (ranked from highest to lowest risk)
- clarithromycin
- erythromycin
- telithromycin

Tyrosine kinase inhibitors:

- dasatinib
- lapatinib
- nilotinib
- sunitinib

Miscellaneous:

- alfuzosin
- flecainide
- fosphenytoin
- indapamide
- methadone
- ranolazine
- tacrolimus
- vardenafil

Table 3: Medium risk QTc prolonging medications

2007. University of Illinois College of Pharmacy**Drug-induced QT prolongation (Part 2): a focus on select medications**.http://dig.pharm.uic.edu/faq/2013/Feb/faq2.aspx

Low Risk QT Prolonging Medications

Low Risk Medications		
Psychotropics: SSRIs (ranked from highest to lowest risk)*:* • citalopram • escitalopram • fluoxetine • paroxetine • sertraline TCAs • amitriptyline • clomipramine • desipramine • doxepin • imipramine • nortriptyline • protriptyline • trimipramine	*Antimicrobials:* Azoles (ranked from highest to lowest risk)*:* • itraconazole • ketoconazole • Fluconazole Miscellaneous: • atazanavir • azithromycin • ciprofloxacin • SMX/TMP	*Antiemetics:* • dolasetron • palonosetron • ondansetron • granisetron *Miscellaneous:* • mexiletine • propafenone • solifenacin

Table 4: Low risk QTc prolonging medications

2007. University of Illinois College of Pharmacy**Drug-induced QT prolongation (Part 2): a focus on select medications**.http://dig.pharm.uic.edu/faq/2013/Feb/faq2.aspx

Antipsychotics

- All antipsychotics have the ability to prolong the QT interval; however some have a higher risk of TdP than others.

ANTIPSYCHOTICS	
Thioridazine	25-30
Ziprasidone	5-22
Pimozide	13
Clozapine	8-10
Iloperidone	9
Haloperidol	7
Quetiapine	6
Risperidone	0-5
Olanzapine	2
Asenapine	2-5
Aripiprazole	0

Table 5: Lists Antipsychotics From highest to lowest QTc prolongation in ms

Gören JL, Dinh TA. Psychotropics and sudden cardiac death. R I Med J (2013). 2013;96(3):38-41.

Antipsychotics & QTc Prolongation

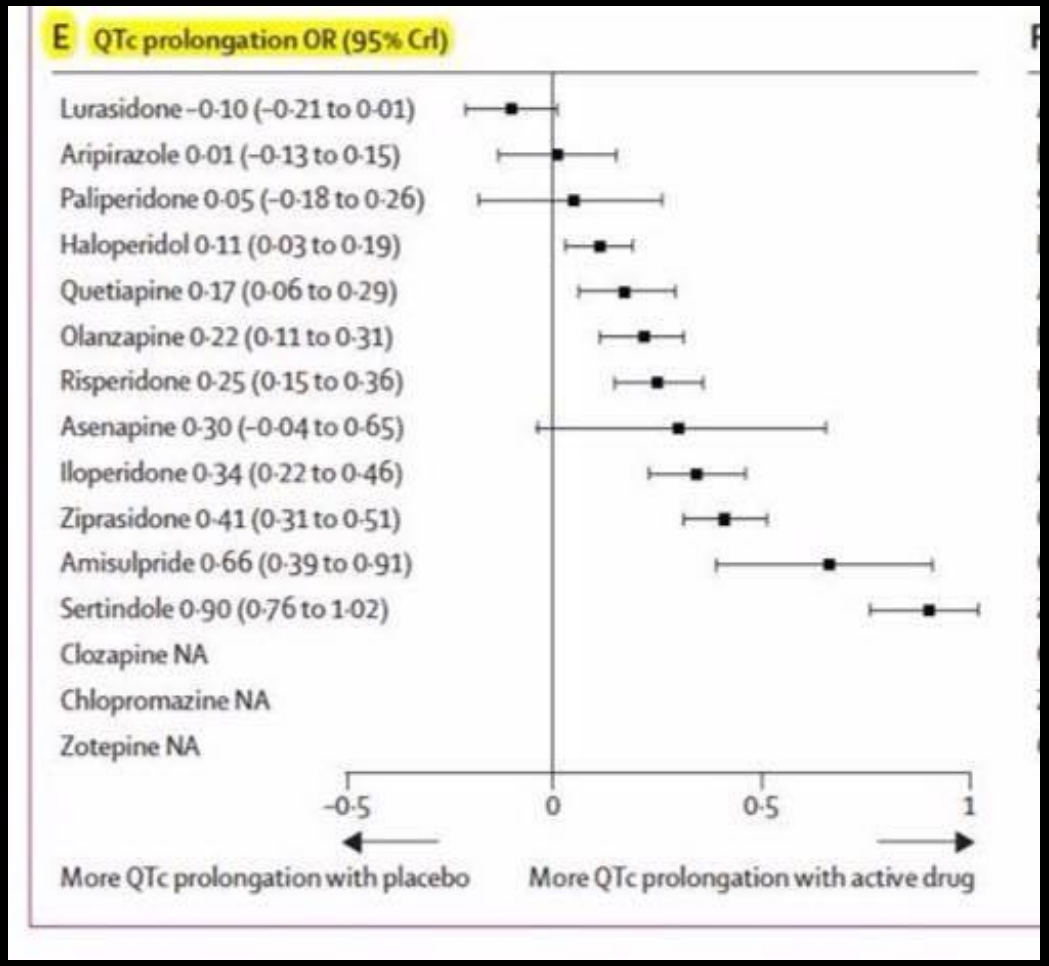
Drug	QTc Prolongation	QTc (Bazett) prolongation compared to baseline in ms (n)	Reported cases of TdP in FDA database
Ziprasidone	++	+9.7 (n=3095)	+++
Quetiapine	+++	-2 to +19.7 (n=312)	++
Risperidone	++	+2 to 11.6 (n=185)	+
Clozapine	++	+10 (n=13)	+
Paliperidone ER	0	+1.7 to 3.7 (n=1300)	Not Reported
Olanzapine	+	-4.5 to +8.4 (n=1342)	Not Reported
Aripiprazole	0	-4 to -3.5 (n=828)	Not Reported

Table 6:Relative risk of QTc prolongation, the ranges reported in the literature and the relative incidence of QTc prolongation in the literature.

Wenzel-Seifert K, Wittmann M, Haen E. QTc prolongation by psychotropic drugs and the risk of torsades de pointes. Dtsch Arztebl Int. 2011; 108(41): 687-93.

Antipsychotics

Figure 1: Forest plot for effect sizes of antipsychotic drugs compared with placebo for QTc prolongation



Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013;382(9896):951-62.

Challenges in Community Pharmacy

- ECG unavailable (no baseline QTc information)
- Electrolyte monitoring/ lab values unavailable
- Renal function often unknown
- Polypharmacy... pharmacist may not be aware of all drugs the patient is taking

Community Pharmacy: Minimizing QTc Prolongation Risk

- Suggest alternative therapy (use drug with lowest risk of TdP within the same class)
- Discontinuation of unnecessary drugs (Indication?)
- Identify drug interactions (especially those involving the CYP450 system)
- Educate patients on signs/symptoms (syncope, palpitations) and risk factors of QTc prolongation

Community Pharmacy: Minimizing QTc Prolongation Risk

- Assess compliance, is there a chance the patient may take a higher dose than prescribed?
- Encourage avoidance of polypharmacy when possible
- Utilize MedsChecks to develop a complete patient history

Community Pharmacy: Minimizing QTc Prolongation Risk

- **Screen patients for risk factors for prolonged QTc interval**, such as congenital long QT syndrome, family history of cardiac conduction abnormalities, and previous occurrences of medication-mediated QTc prolongation.

Community Pharmacy: Minimizing QTc Prolongation Risk

- Assess patient's global risk taking into consideration which medications can be altered/changed and which medications cannot. *Ie. Identifying the most appropriate care provider to fax recommendations to*
- Always document the prescriber's clinical rationale for maintaining or altering the patient's drug therapy

2007. University of Illinois College of Pharmacy**Drug-induced QT prolongation (Part 2): a focus on select medications**.http://dig.pharm.uic.edu/faq/2013/Feb/faq2.aspx

Systematic Approach To Managing Potential QTc Prolongation

Computer alert or drug interaction warning of drug-induced QT prolongation and TdP

Risk assessment - the patient
What risk factors are present in the patient?
Which risk factors are modifiable?

Risk assessment - the drug(s)
What is the overall risk of QT prolongation and TdP with the drug(s)?
Which of the patient's other medications are of concern?

What is my patient's Global risk, taking in consideration all risk factors?

Risk minimization
Identify risk factors and address those that are modifiable
Within the same class, utilize drugs that carry the lowest risk of drug-induced TdP
Consider alternative treatments with lower TdP-inducing potential

Monitoring
Suggest ECG at baseline and after drug administration
Continued risk factor minimization such as dosage adjustments and drug interaction avoidance

So What Do we do With Mrs.Bee?

- She has been prescribed Azithromycin from a walk-in clinic for potential Community Acquired Pneumonia.
- Mrs. Bee presents with a number of risk factors for QTc prolongation, including older age, female sex, and psychiatric and medical comorbidities that require QTc prolonging medications (Paroxetine and Quetiapine).

So What Do we do With Mrs.Bee?

- While reviewing Mrs. Bee's medications, you realize she is running low on her quetiapine.
- During the Medication review, Mrs. Bee says that if she misses her medication, she would take them when she remembered. If she could not remember if she took her pills, she would take them again.

So What Do we do With Mrs.Bee?

- Azithromycin + Quetiapine: Category X interaction for QTc Prolongation
- Levofloxacin and Moxifloxacin have same interaction
- Suggest an antibiotic(s) that does not have QTc prolongation risk
- Doxycycline, Amoxicillin, Amoxicillin-Clavulanate all reasonable options

So What Do we do With Mrs.Bee?

- Mrs. Bee could benefit from blister packing her medications
- Suggestion could be made to either change or alter dosages of Quetiapine or Paroxetine (Risk factor D for QTc prolongation)
- Mrs. Bee must be educated on signs/symptoms of QTc prolongation

Summary

- QT prolongation leading to TdP is a relatively rare potential side effect of many drugs.
- Most common affiliated classes of drugs include: antiarrhythmics, antidepressants, antibiotics, and antipsychotics.
- It is important to consider patient risk factors as well as specific properties of the drugs.
  - i.e. patients with 2 or more risk factors and 2 or more drugs with the risk of TdP

THE ART AND SCIENCE OF MANAGING ANTIPSYCHOTIC MEDICATIONS

Putting Antipsychotic Medication Risks into Perspective

- It was often viewed that QT prolongation was a significant safety concern with antipsychotics, but these concerns do not show up in clinical data.

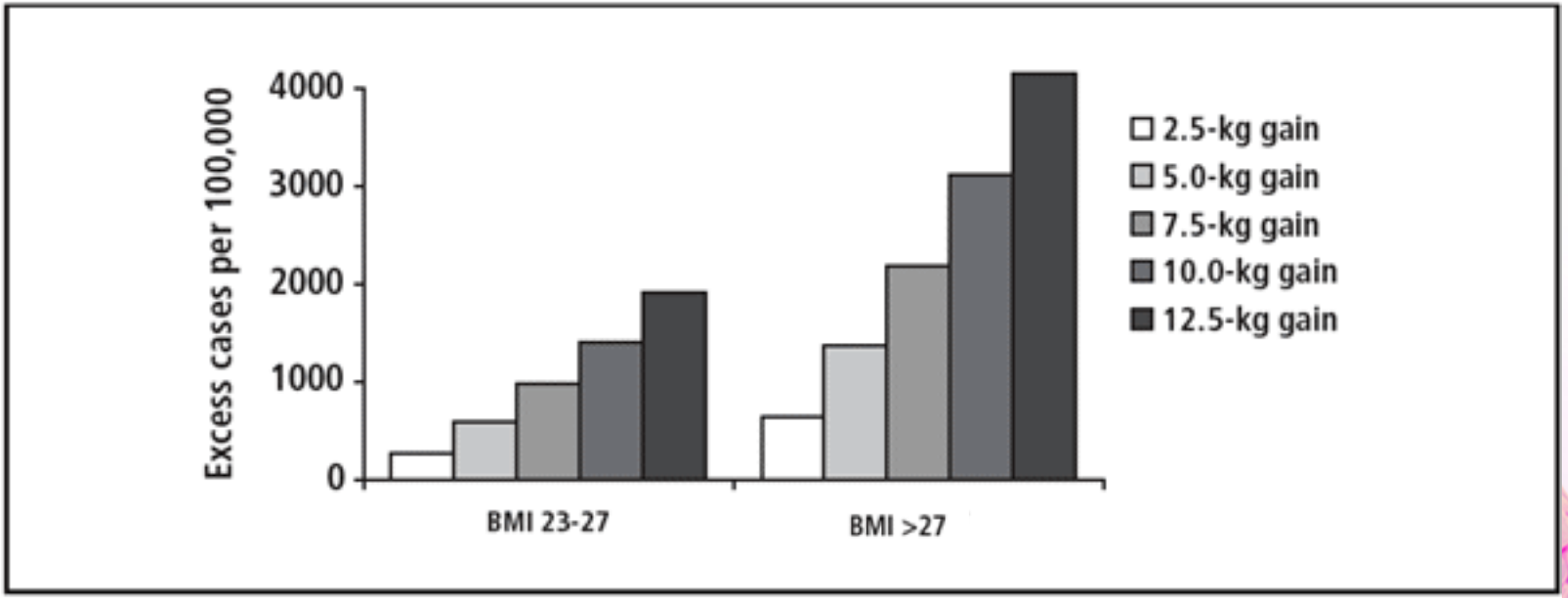
- Other AEs, such as weight gain, insulin resistance, hyperglycemia, hyperlipidemia, and CHD, are emerging in clinical data as a concern with use of these agents.

- The cardiovascular risks associated with antipsychotic treatment highlight the importance of **primary prevention**.

Metabolic Syndrome and Long-term Risk Factors

Diabetes

Figure 19. Impact of antipsychotic-induced weight gain on the number of excess cases of IGT/diabetes over 10 years, estimated based on Framingham data.[69]



IGT=impaired glucose tolerance.

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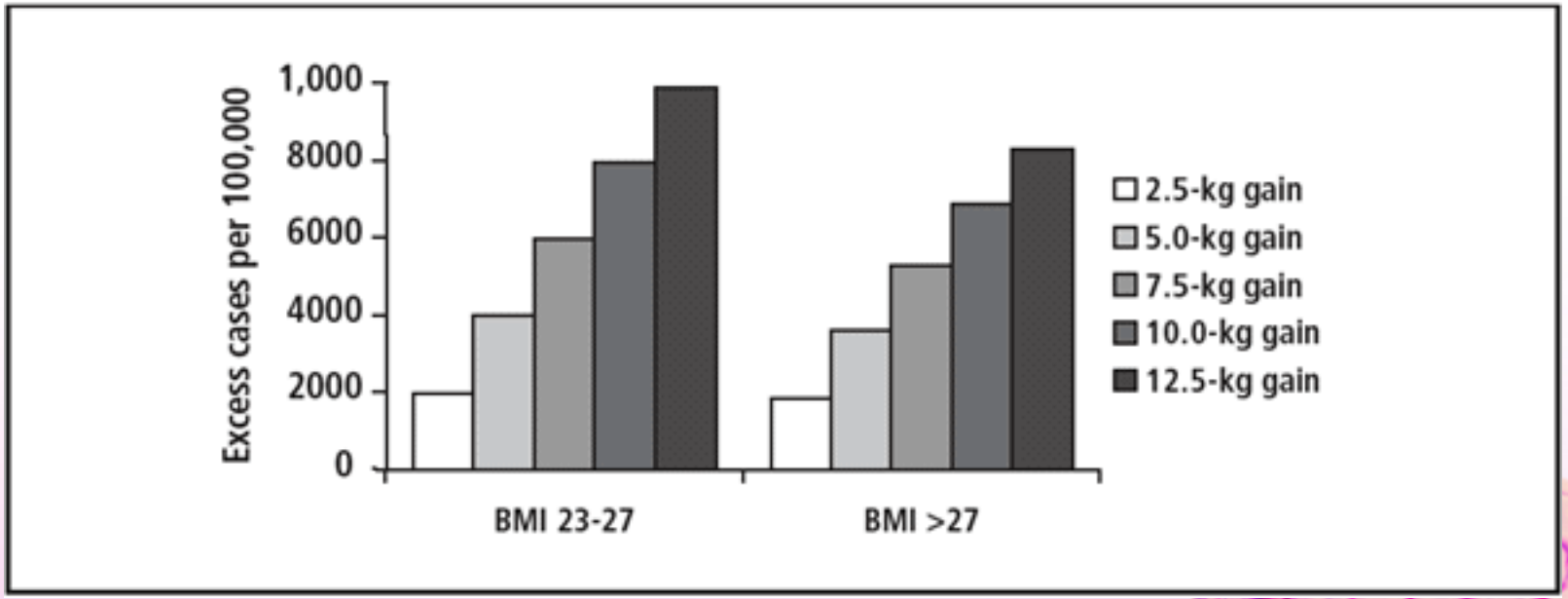
Metabolic Syndrome and Long-term Risk Factors

Hypertension

Figure 20. Impact of antipsychotic-induced weight gain on the number of excess cases of hypertension over 10 years, estimated based on Framingham data.[69]



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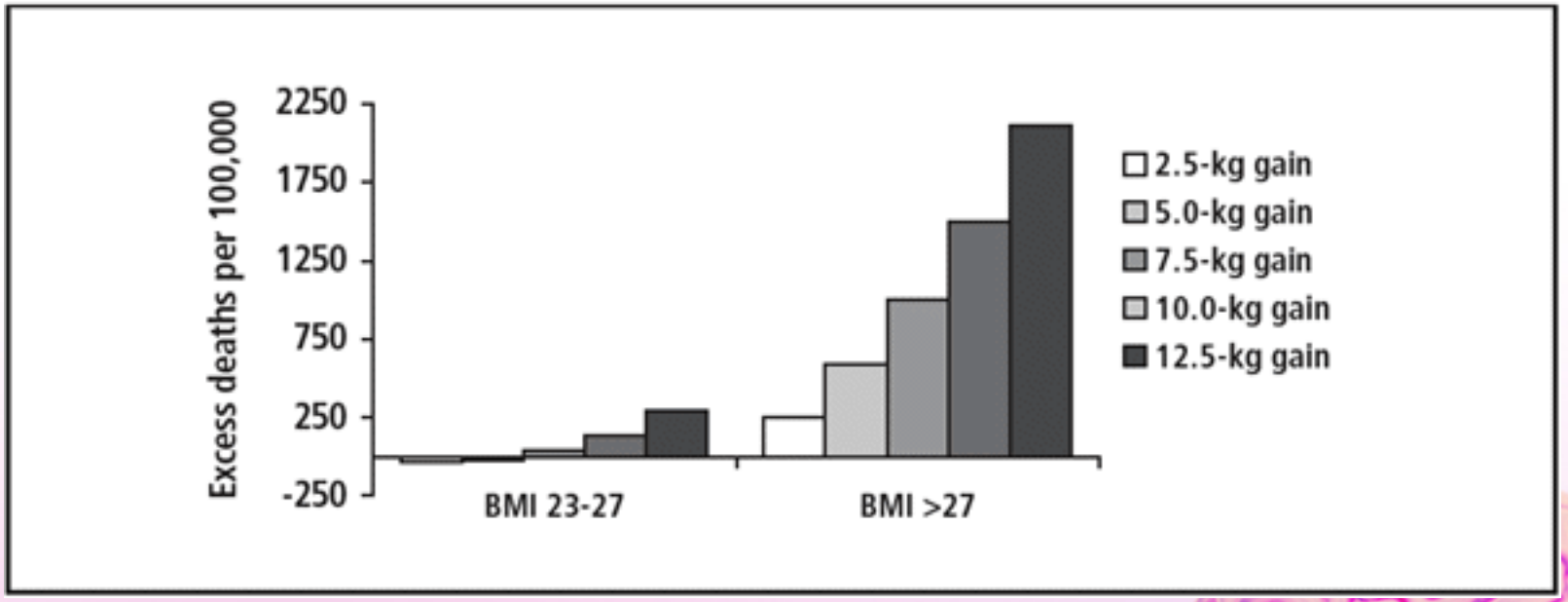
Metabolic Syndrome and Long-term Risk Factors

Mortality

Figure 21. Impact of antipsychotic-induced weight gain on the number of excess fatalities over 10 years, estimated based on Framingham data.[69]



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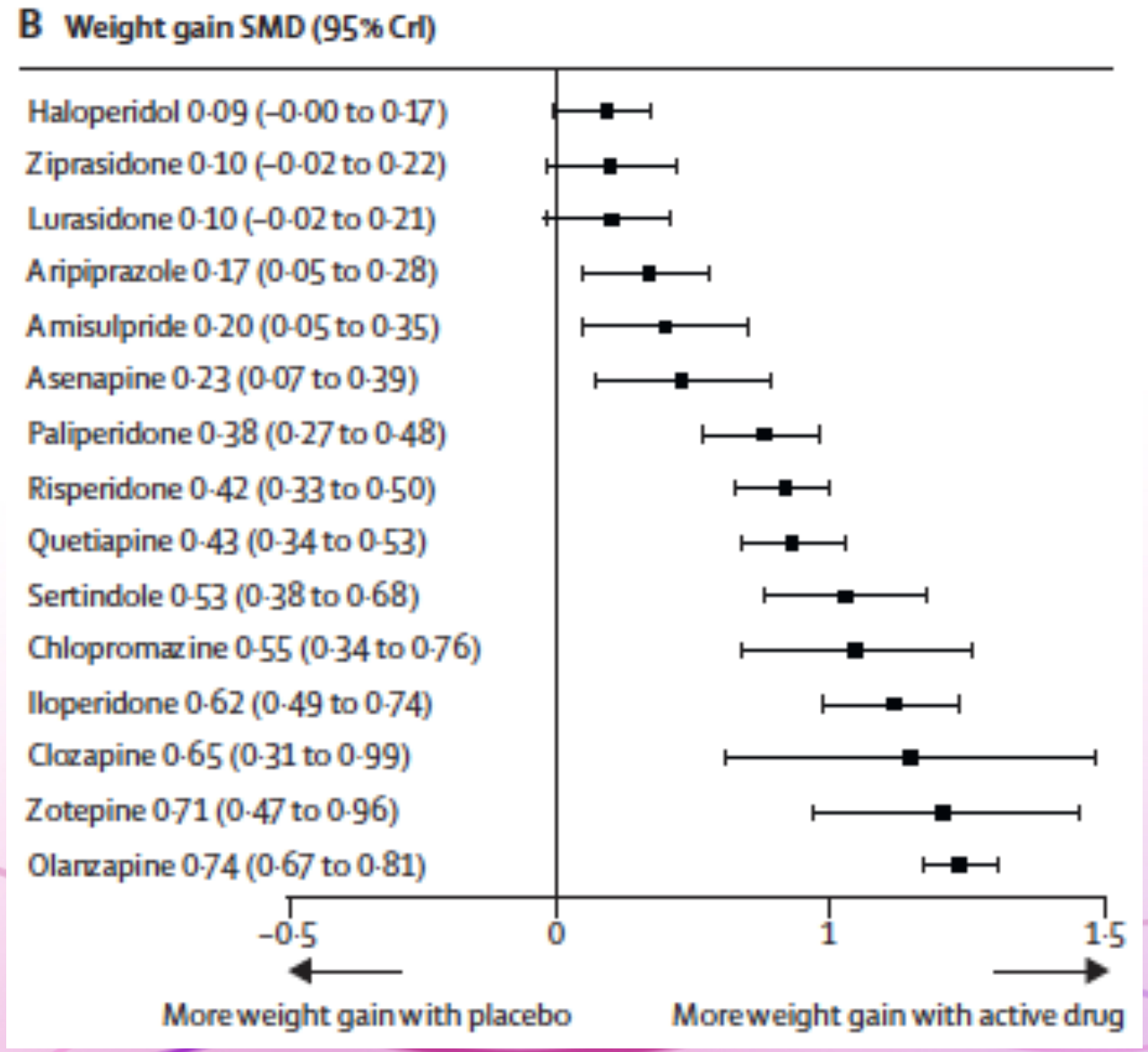
Side Effect Hierarchies for Psychosis/Schizophrenia



Leucht,S. et al. 2013

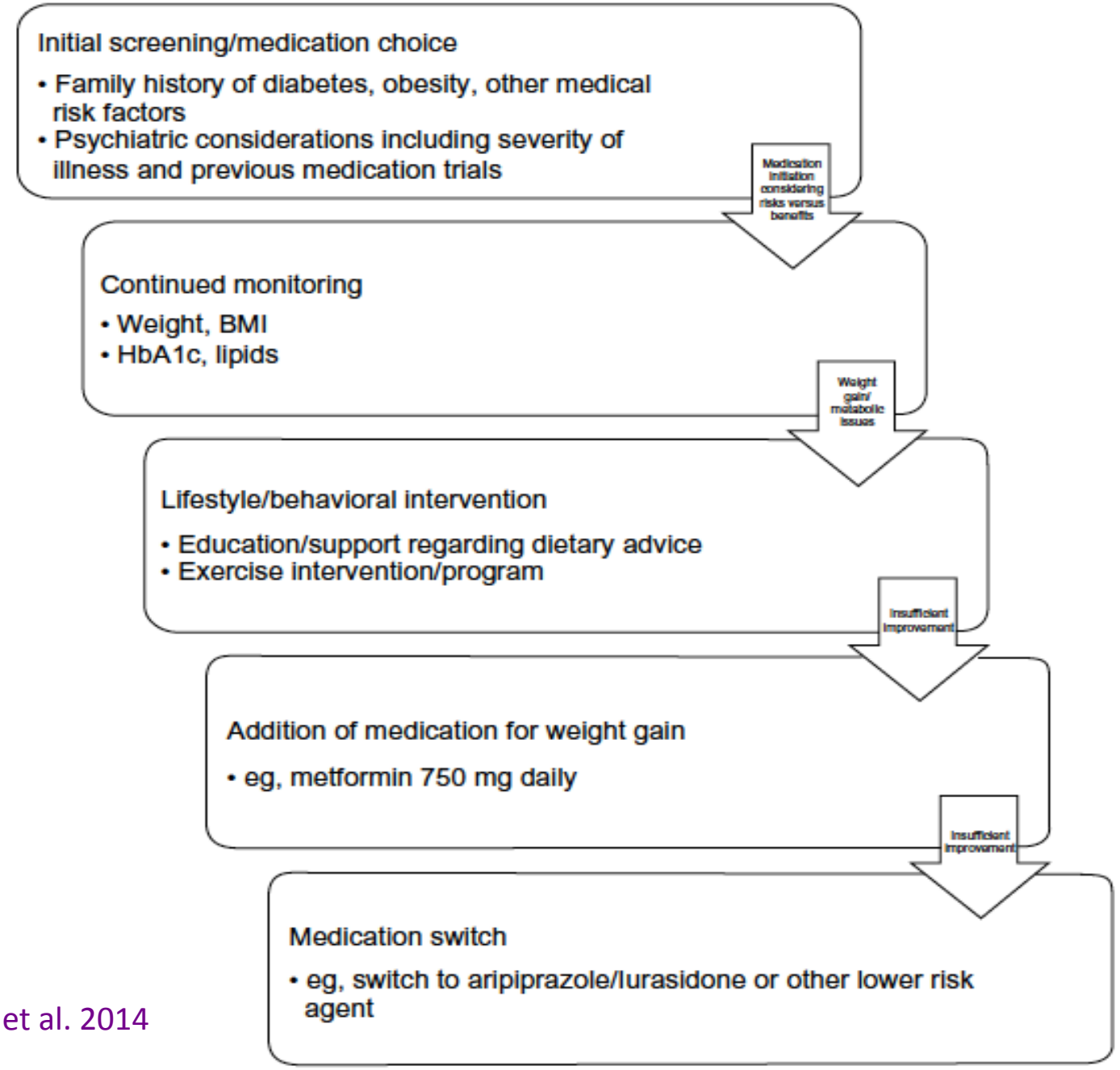


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Figure 1 Metabolic and weight gain treatment and monitoring algorithm.
Abbreviations: BMI, body mass index; HbA1c, glycosylated hemoglobin.

Pharmacist Involvement with Antipsychotic Therapy

Table 9. Recommended frequency of metabolic screening and follow-up monitoring in patients receiving antipsychotic therapy.[6]

Measurement	Baseline	4 Weeks	8 Weeks	12 Weeks	Every Quarter	Every Year	Every 5 Years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
BP	X			X		X	
FPG	X			X		X	
Fasting lipid profile	X			X			X

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Pharmacist Involvement with Antipsychotic Therapy

- Adherence
  - Adequate medication trial and appropriate dose adjustments
- Identifying the Switch/Identifying add-on therapy
- Monitoring side effects at refills
- Primary prevention/metabolic screening
- Lifestyle advice: smoking cessation, diet, and exercise
- Polypharmacy

Summary

- Emphasis on patient-centered care when it comes to managing antipsychotic therapy
- Being able to identify multiple indications (on/off label) for use of antipsychotic drug therapy
- Comparative efficacy exists across agents and classes
- Focus for adjustment of therapy comes from adverse events
- Pharmacists have the opportunity to play a major role in the patient's success in using antipsychotic therapy and improving QOL