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Applied Translational Medicine

Incorporating Early Assessments of Cardiovascular and CNS Safety into Early Clinical Studies

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Objectives of Early Clinical Research

1. Establish safety
   - Understanding the maximum tolerated dose or maximum feasible dose in human
   - Translation of nonclinical to clinical observations
   - Unexpected safety observations
2. Understand pharmacokinetics (dose-exposure)
3. Explore potential for efficacy
   - Clinical outcome measures
   - Biomarkers (target engagement, mechanism-of-action)

CNS Safety Assessment

Why Monitor CNS Safety?

- Early decision-making
- Critical for tolerability profile and appropriateness of patient populations
- Product differentiation

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CNS Side-effects from Non-CNS Drugs

Examples:

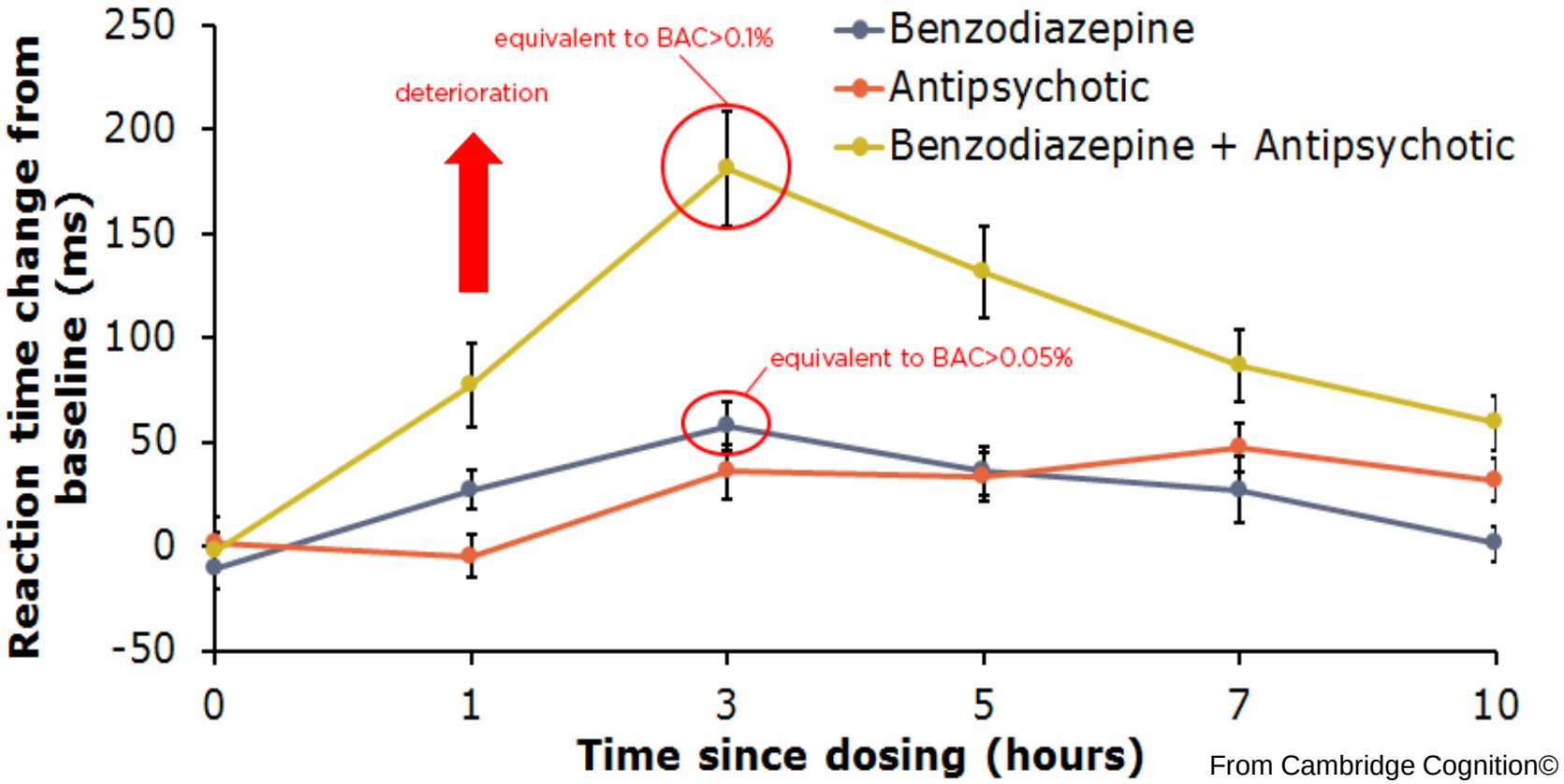
- Cardiovascular
  - Beta-blockers for hypertension can result in insomnia, depression, nightmares
  - ACE inhibitors: dizziness, drowsiness, light headedness
- Respiratory
  - Anti-histamines. non-sedating do not cross the BBB
- Anti-viral
  - Non-nucleoside reverse transcriptase inhibitors, like efavirenz (Sustiva®), rilpivirine (Edurant®), can result in mood changes, anxiety, dizziness, sleep disturbance (insomnia, nightmares), and even psychosis
- Immune modulators
- Metabolic disease

Unwanted CNS Activity

- On-target, wrong tissue
  - Anti-histamines
    - Sedating: can cross BBB
    - Non-sedating: can't cross BBB

- Off-target
  - Neurotransmitter receptors (dopamine, serotonin, GABA and acetylcholine)
  - Efanirenz (NNRTI) interacts with **5-HT$_{2A/C}$ receptors**, serotonin & dopamine reuptake, monoamine transporter, and GABA$_A$ receptors

Polypharmacy. Potential for Synergism



From Cambridge Cognition©

Alone the drugs had a minimal effect, but in combination the negative effect on reaction times was equivalent to having a blood-alcohol level of 0.1%.

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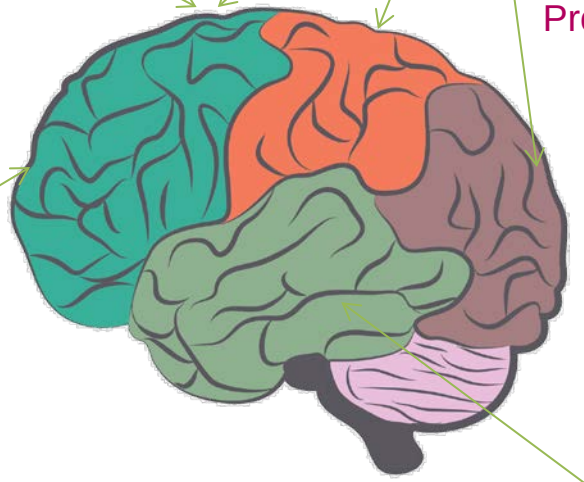
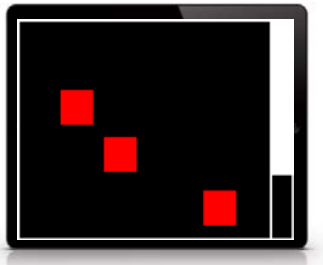
Cambridge Cognition (Computerized Tests)

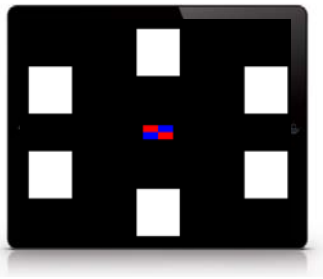
Reaction Time

Rapid Visual Information Processing





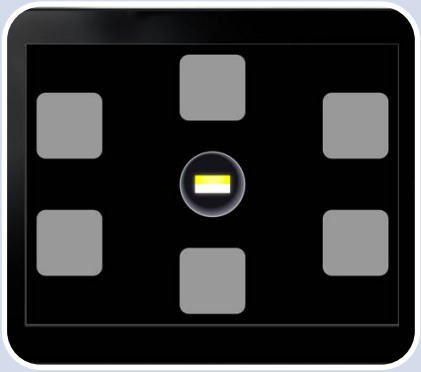
Spatial Working Memory

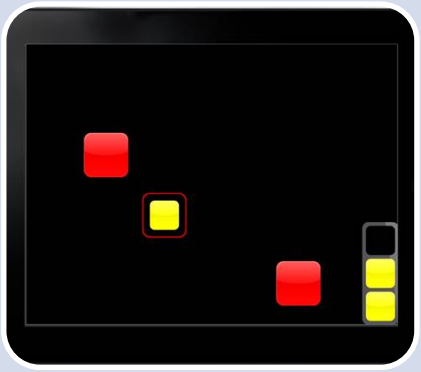


Paired Associates Learning

From Cambridge Cognition©

Clinical Trial Information System (CTIS) Profile





Reaction Time (RTI)

Assay for mental response speeds as well as movement times and accuracy

Paired Associates Learning (PAL)

A visual associative memory and new learning task to accurately assess episodic memory

Spatial Working Memory (SWM)

Requires retention and manipulation of visuo-spatial information. Measures working memory and executive function

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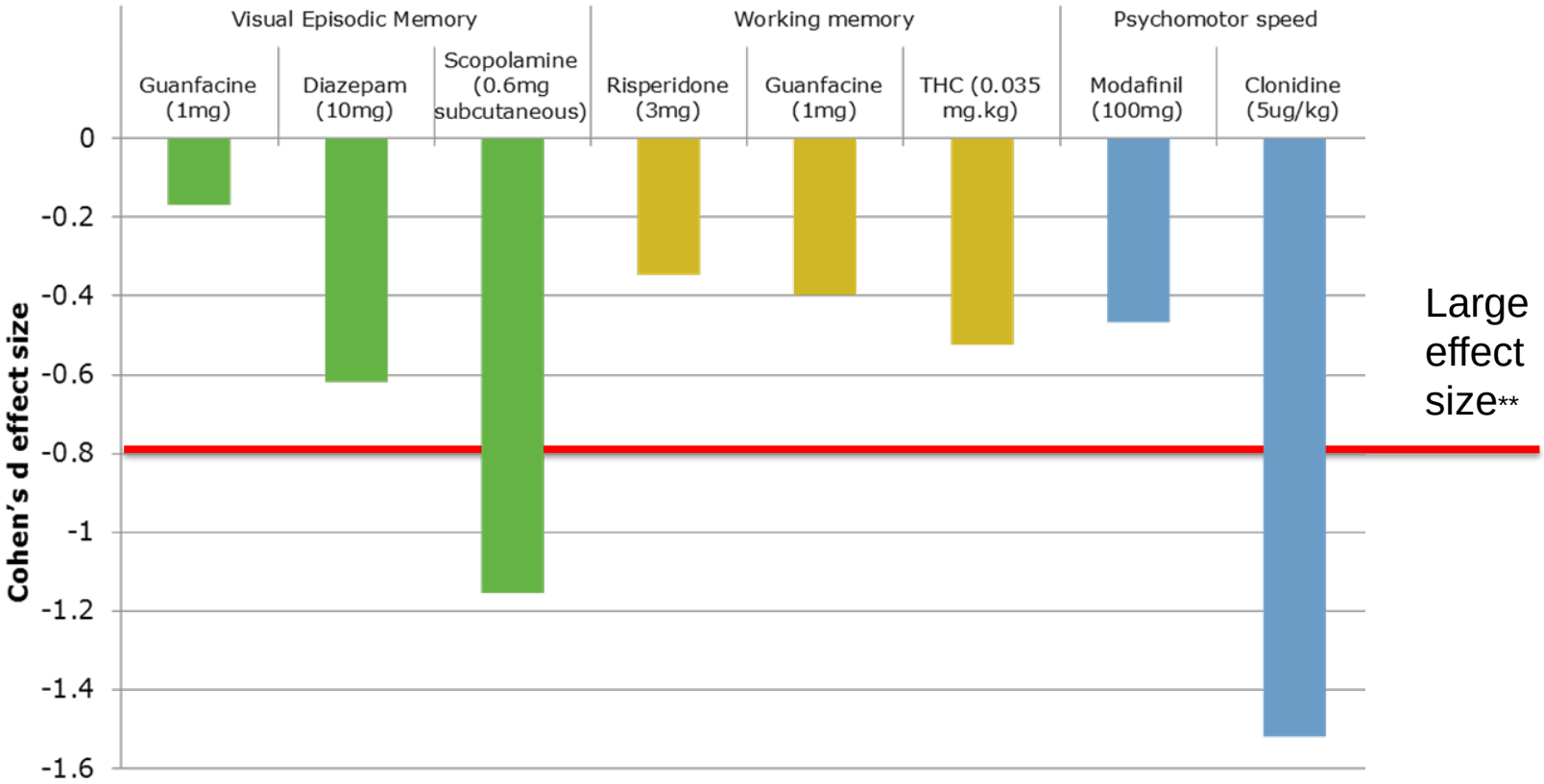
Validity and Sensitivity

	Sensitivity to Cognitive Impairment	Sensitivity to Cognitive Enhancement	Validity
Spatial Working Memory (SWM)	Tyrosine depletion in healthy subjects (d=0.42) (Harmer et al., 2001).	Methylphenidate in healthy subjects (d=1.51) (Elliot et al., 1997).	Owen et al., 1990; Manes et al., 2002; Owen et al., 1996
Paired Associates Learning (PAL)	Scopolamine in healthy Subjects (d=1.12) (Rusted & Warburton, 1988). Rosiglitazone (no placebo) in diabetes (d=0.69) (Ryan et al., 2006).	Phenserine in patients with Alzheimer's disease (d=0.46) (Greig et al., 2005).	Owen et al., 2002; Swainson et al., 2001; de Rover et al., 2011
Reaction time (RTI)	Clonidine in healthy subjects (d=1.52) (Jakala et al., 1999).	Caffeine in healthy volunteers (d=0.44) (Attwood et al.,2007).	Robbins, 2002

Published data show that drugs can improve or impair performance in these tests

Sensitivity of Outcome Measure



- **Effect size's greater than 0.8 are considered to be "large" and would be expected to be clinically significant, and require serious evaluation by the clinical study team.**

**Cohen (1988), Kraemer and Kupfer (2006)

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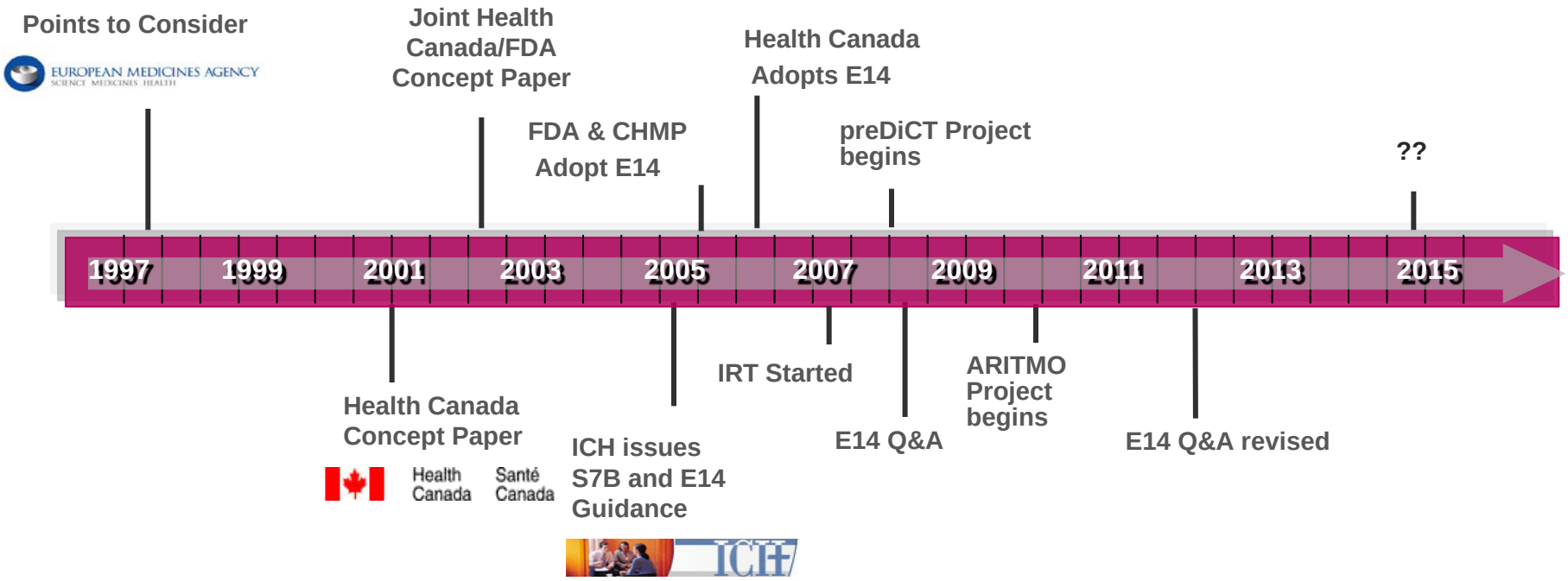
Key Properties of CTIS Profile

- Summary
  - Three tests included in battery covering a wide range of cognitive domains
  - Takes a little over 20 minutes to complete
  - Can be used repeatedly (especially when test sessions are well spaced out)
  - Change with age is well documented
  - Test performance correlates with real life cognitive performance
  - Tests performance can be improved or impaired by drug treatment
  - Can detect clinical significant sized effects as well as sensitive to more subtle changes
  - Effects on peripheral mechanisms have been shown to influence test performance

Cardiovascular Assessments

The Evolution of Cardiac Safety Testing



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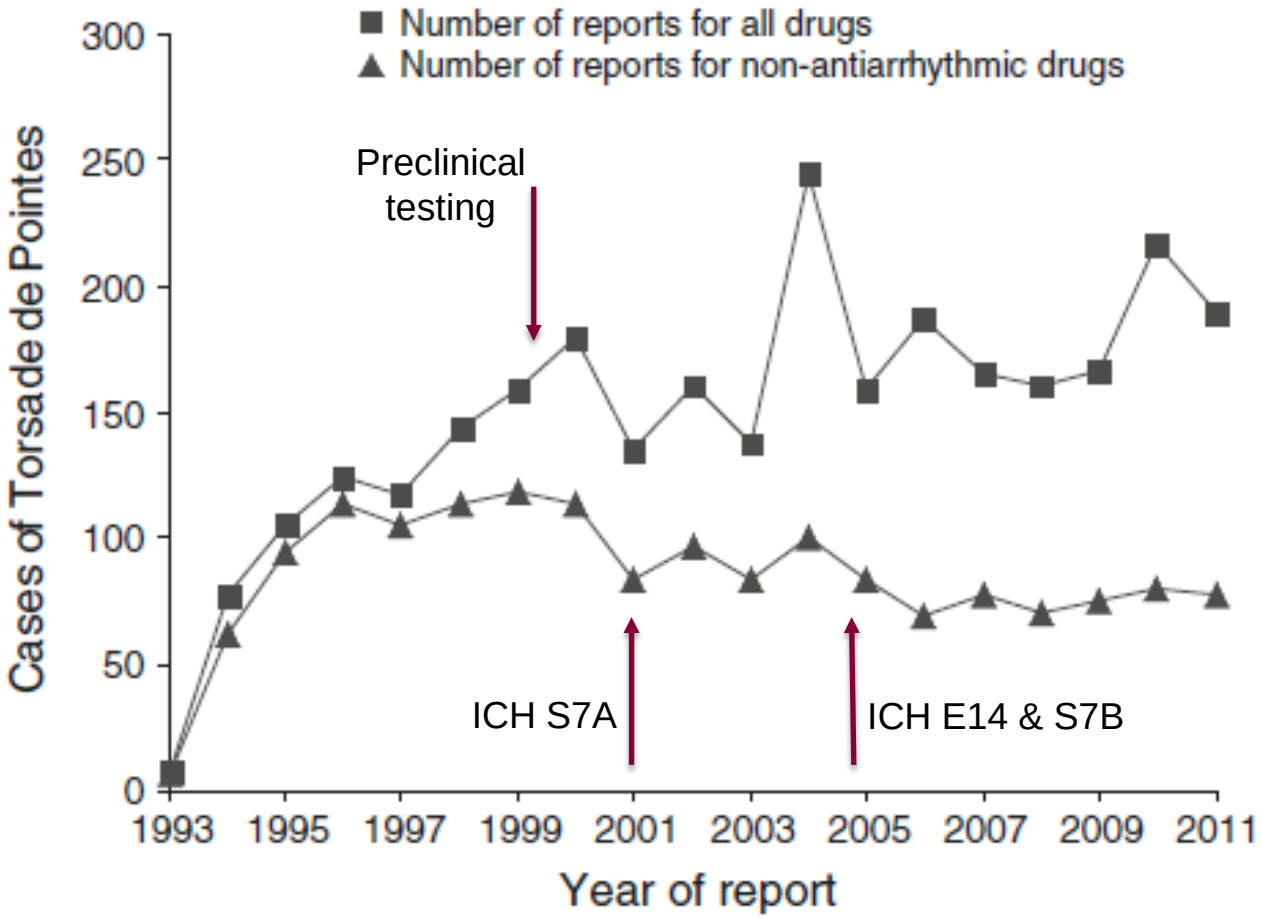
Cases of Torsades de Pointes



Annual number of spontaneous reports of Torsade de Pointes received by the US FDA Adverse Event Reporting System, Stockbridge et al. Drug Safety 2013;36:167-182

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Current Regulatory Guidance (Nonclinical)

- ICH S7A (Safety Pharmacology)
  - Cardiovascular system
    - Core battery: blood pressure, heart rate, ECG
    - Follow-up: cardiac output, ventricular contractility, vascular resistance
- ICH S7B (QT prolongation)
  - Ikr (hERG) assay
  - *In vivo* (telemetry) QT assessment
  - Chemical/pharmacological class
  - Integrative risk assessment

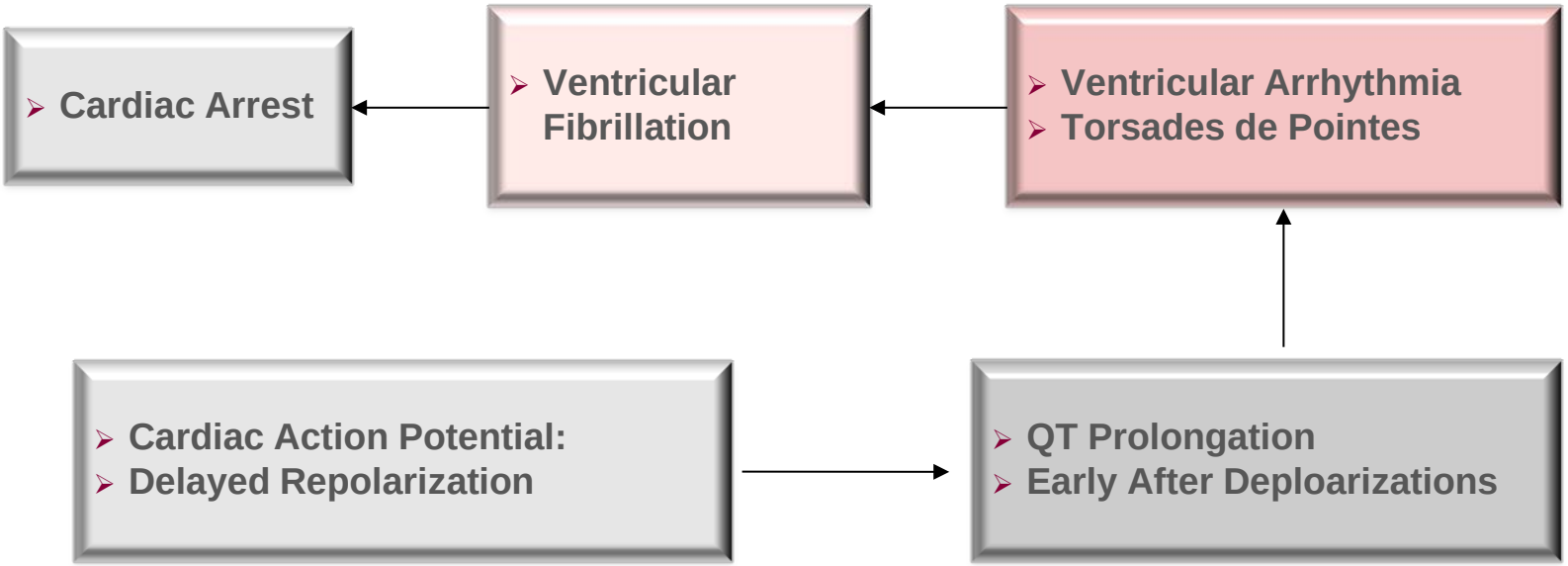
Current Clinical Cardiac Safety Guidance

- ICH E14 (QT/QTc prolongation and proarrhythmic potential)
  - Specifies Thorough QT/QTc study
    - Threshold for regulatory concern: 5 ms change in QTc
    - Typically done in healthy subjects
    - Positive control (often moxifloxacin)
- E14 Questions and Answers (2008)
  - Provided clarifications
    - Positive control to establish assay sensitivity (lower bound of one-sided 95% CI must be above 0 ms)
    - Who should read ECGs (must be blinded, cardiologist over-read acceptable)

Current Debate

- Does the TQT truly predict a compound's proarrhythmia potential?
- There have been tremendous advancements in both pre-clinical and early clinical monitoring of arrhythmia potential since 2005. How does this:
  - Change proarrhythmia evaluation pre-clinically and/or clinically?
  - Change the need for a TQT?
- What has been the impact of ICH E14 and S7B on drug development? Is it worth the cost?
- What does a positive TQT really mean?

Relationship of QT Prolongation and Human Risk



From: Morimoto and Fox (2011) In: *Principles and Practice of Pharmaceutical Medicine (Edwards, Fox and Stonier,* ed.) 3rd ed. Wiley-Blackwell

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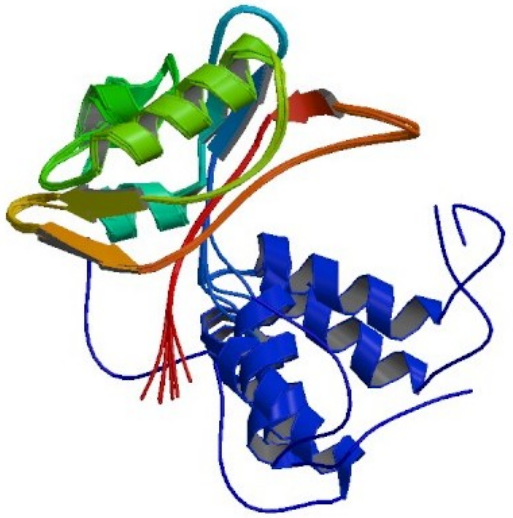
Is there an Alternative to Thorough QT Studies?

Increase Nonclinical Testing

- Comprehensive In vitro Proarrhythmia Assay (CiPA) Initiative
  - Ion channels
    - Perform comprehensive tests (hERG plus 3 to 6 additional cardiac channels)
  - Stem cell-derived human cardiomyocytes
  - In silico modeling
- Result: update ICH S7B



Early Clinical Cardiac Safety Evaluation

- Proposal:
  - Include intense ECG monitoring to early Single Ascending Dose (SAD) and Multi Ascending Dose (MAD) studies
    - Pool data from different dose levels to evaluate concentration response relationship
    - Typically during SAD and MAD studies the highest doses are given allowing for better concentration response modeling

Early Clinical Cardiac Safety Testing

- Consortium for Innovation and Quality in Pharmaceutical Development/Cardiac Safety Research Consortium (IQ/CSRC)
  - Look at six marketed drugs, 5 positive QT signal and 1 negative control
  - Two doses: 10-12 ms and 15-20 ms
    - Ondansetron, dofetilide, quinine, dolasetron, moxifloxacin
    - Levocetirizine (negative control)
  - SAD-like study
- QT assessment criteria: The upper bound of the two-sided 90% confidence interval (CI) of the projected placebo-corrected delta QTcF is above 10 ms at the observed peak plasma level of the drug
- Sensitivity and specificity of measuring QT prolongation
- Concern over potential false negatives (regulators) and false positives (sponsor)

IQ-CSRC Study

- 3 period, randomized, placebo-controlled study
- Incomplete block design used
  - Each study drug administered to 9 subjects and placebo to 6 (total n=20)
- Continuous 12-lead ECGs with replicate ECGs extracted
- Exposure response analysis performed
  - Evaluate relationship between plasma concentration and placebo corrected, change-from-baseline QTc ($\Delta\Delta$QTc)
- "QT positive" if the UB of the 2-sided 90% CI of the predicted placebo-corrected ΔQTcF is above 10 ms at the observed geometric mean C_{max} of the lower dose of the studied drugs

Darpo et al. (2014) *Ann Noninvasive Electrocardiol* 19, 70-81
Darpo et al. (2015) *Clin Pharmacol Ther* 97, 326-335.

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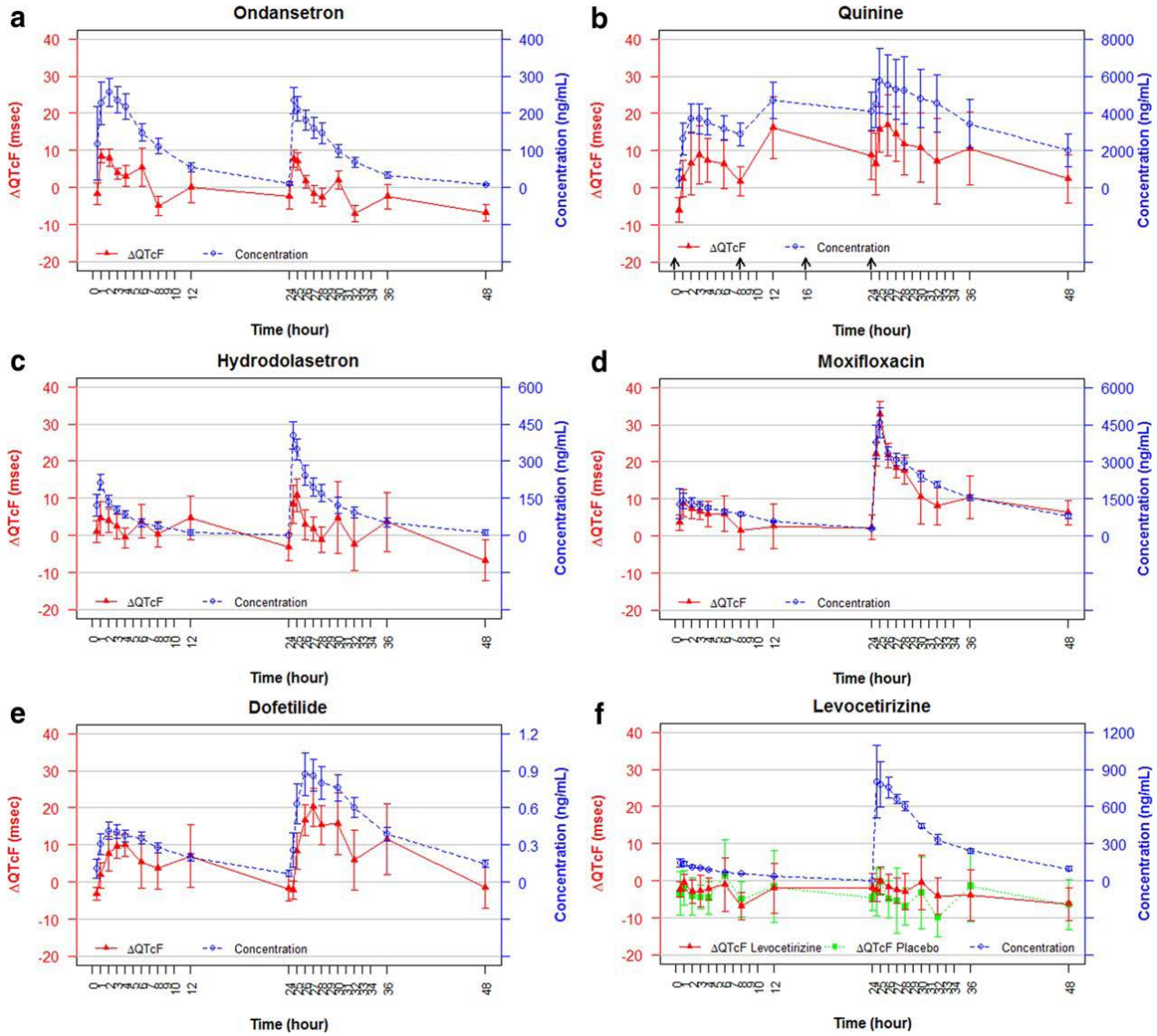
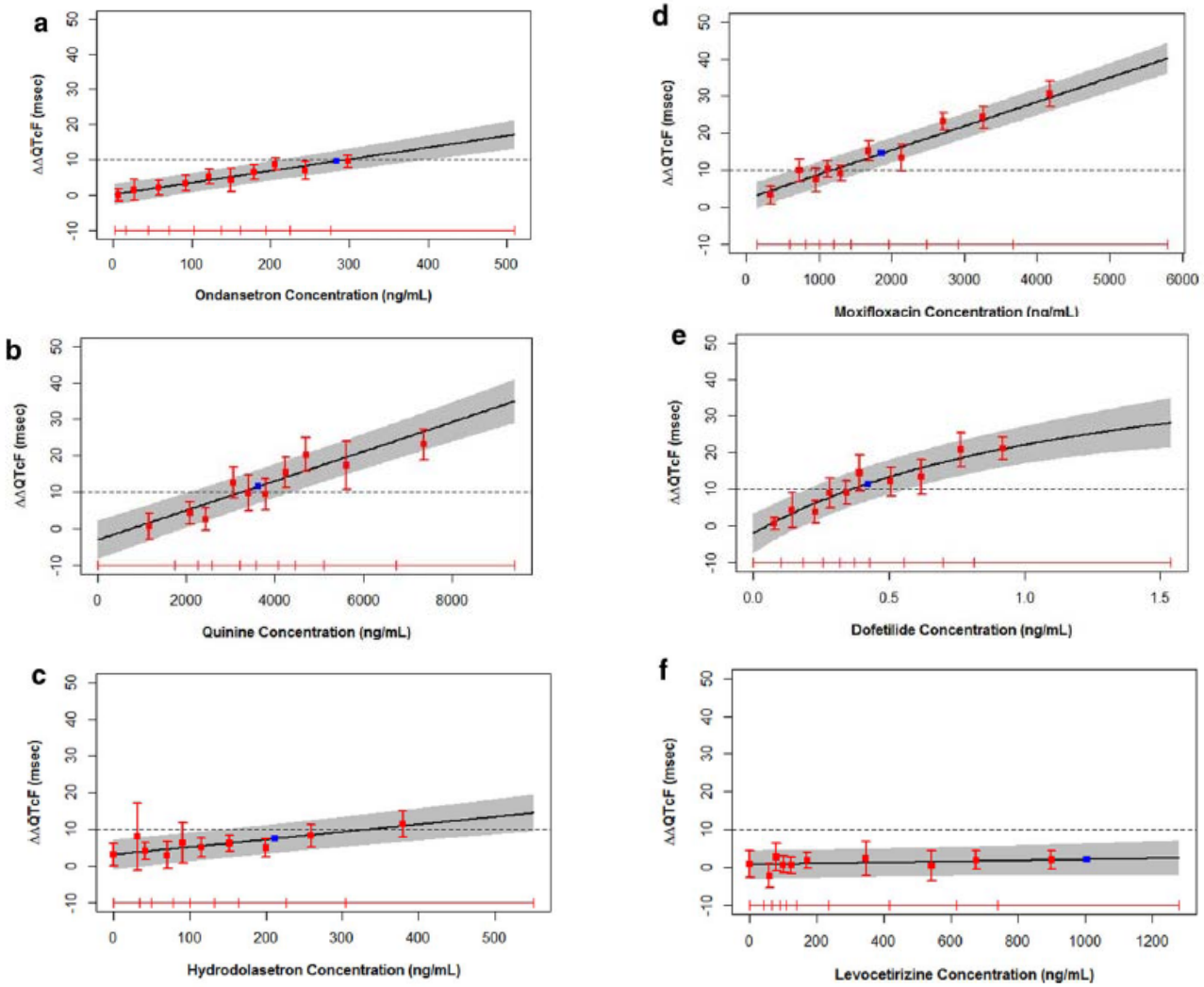
IQ-CSRC: Pharmacokinetics and QT Data



Darpo et al. (2015) *Clin Pharmacol Ther* 97, 326-335

IQ-CSRC Study: Exposure-response Results



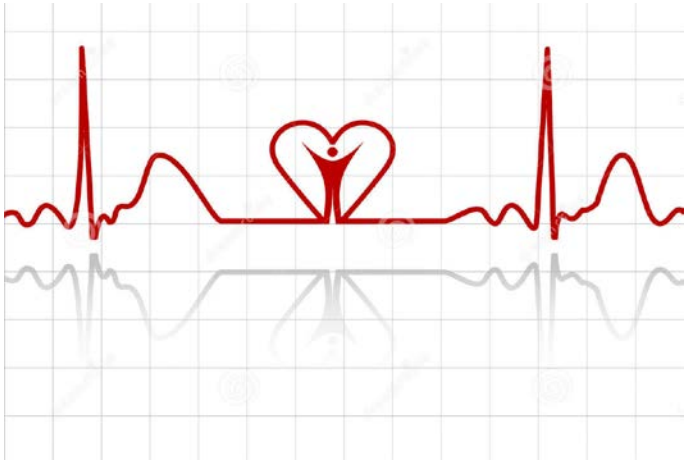
Darpo et al. (2015) *Clin Pharmacol Ther* 97, 326-335

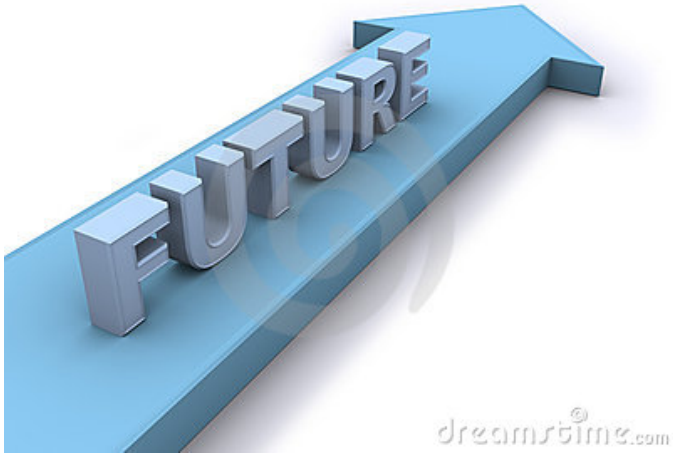
Implications of IQ-CSRC Study

- No positive control in SAD
  - Reassurance against false negatives
  - Risk is small when exposure-response analysis is applied and offset by wide range of plasma concentrations
- Quality test metrics
  - HR stability within time points
  - Reproducible QT/RR curvature
  - Within and between subject variability of QT
  - Time course of QT adaptation to changes in HR
- Study was SAD-like, not exactly like a dose-escalation study
- Group sizes were larger than “typical” SAD

Future Directions

- Need further replication of the IQ-CSRC study
- Pharmacokinetics will drive study design
  - Pronounced accumulation on multi-dosing?
  - Sufficiently high plasma concentration of parent and metabolites?
- Could TQT waiver be obtained?





From: Dreamstime.com

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Questions?
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