Prediction of Adverse Cardiovascular Events of Noncardiovascular Drugs through Drug-Target Interaction Networks

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To the Editor:

Several postmarketing studies of adverse cardiac effects of noncardiovascular drugs have been reported over the past decade. This has included rosiglitazone, an antidiabetic drug. Demonstration of serious complications has been traditionally based on systematic reviews and meta-analyses of clinical trials. However, there is a need to develop new tools to enable the prediction of adverse drug effects in both early discovery and postmarketing stages of drug development. This can be accomplished through drug-target interactions at a systems level.

We recently illustrated how the computational analysis of the Myocardial Infarction Drug-Target Interactome (My-DTome, www.my-dtome.lu) provides comprehensive insights into the complex interplay of cardiovascular and noncardiovascular drugs in the context of specific molecular pathways.[1] My-DTome is organized into modules highly specialized in different clinically relevant molecular processes. This strategy allowed us to elucidate multiple connections between noncardiovascular drugs, for example, fenfluramine, and major cardiovascular perturbations, which go far beyond those predicted by the mode of action of the drugs on specific receptors.

Soon after the recent publication of a report linking varenicline (Chantix) with potential serious cardiovascular complications,[2] we queried My-DTome with this drug and the following results were obtained. Varenicline targets the My-DTome protein CHRNA3 (neuronal acetylcholine receptor subunit alpha-3). CHRNA3 is associated with My-DTome Module 14, which directly interacts with Modules 13 and 16. The latter are highly statistically associated with important cardiovascular-relevant perturbations ($P < 1E\text{-}3$).

Network-based research can complement existing approaches to identifying cardiovascular complications of noncardiovascular drugs, and may guide early stages of novel drug discovery.

References

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2. Singh S, Loke YK, Spangler JG, Furberg CD. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. *CMAJ* 2011; 183: 1359–1366.

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