Enriching real-world evidence insights through QSAR based exposure definitions

Presenter: Vijay Kara
E-mail: vijay.x.kara@gsk.com
Acceptance code: CO176

Gregory E Powell[1], James Lumley[2], Vijay Kara[2], Andrew Bate[2]

[1]GSK, RTP, NC, USA; [2]GSK, London, UK

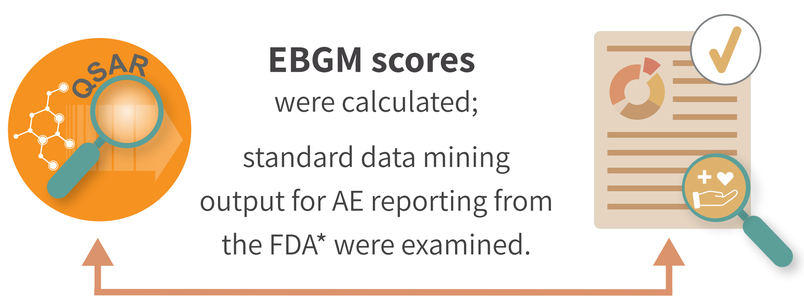
Background

- Real-world evidence (RWE) studies traditionally use simplified definitions of exposure as a binary variable referring to a specific drug or class of drugs (e.g., any versus no use of antihistamines),[1] which does not account for the continuum of structure-activity differences between drugs.[2]
- Despite the utility of quantitative structure-activity relationships (QSAR) models in development (including prediction of drug properties), little work has been done in extending its use to drug exposure definitions in RWE studies.

Objective

We examined chemical predictors from published QSAR adverse event (AE) models incorporating with AE reporting frequencies to show how QSAR based exposure definitions may unlock hidden associations.

Methods

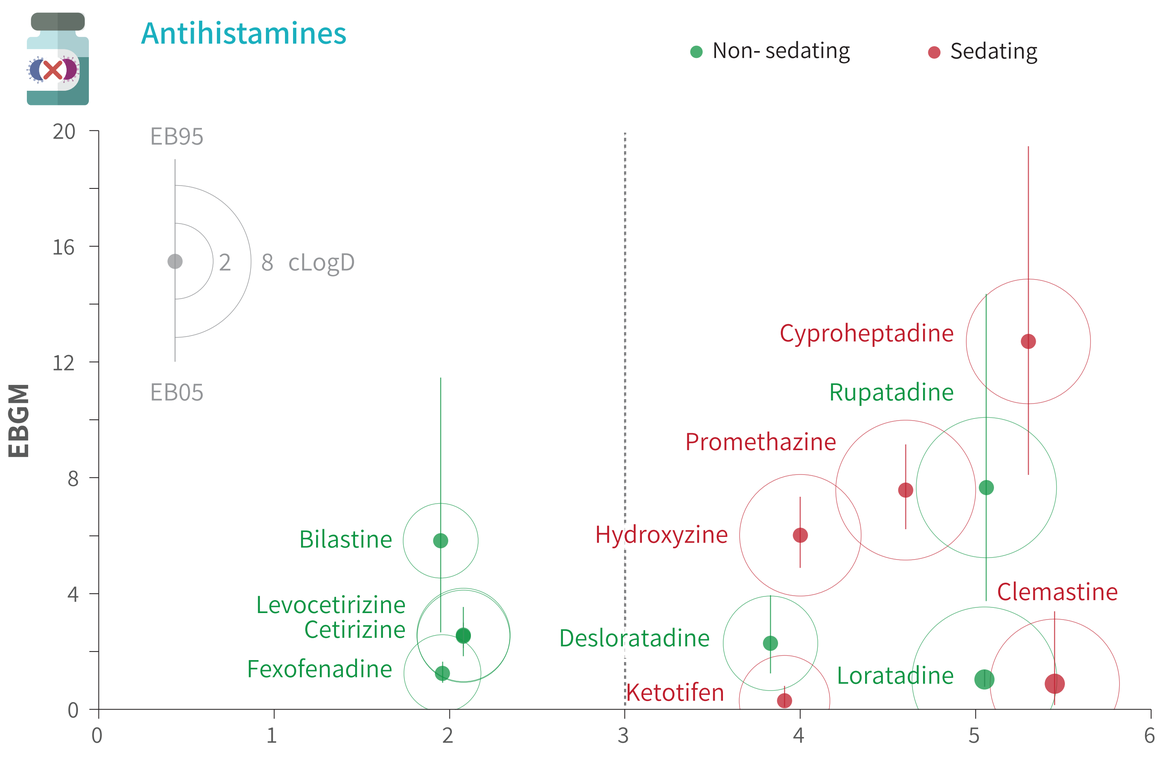


- QSAR drug model results were compared with post-marketing drug safety data to see if the results (e.g., AE reports) correlated.

EBGM, empirical Bayes geometric mean (a measure of association). ***For the 1st quarter of 2022, accessed via a vendor tool. Scores were within the vendor tool, by selecting the relevant parameters (drug-events).

Results

Antihistamines



- For antihistamines with high lipophilicity (cLogP>3), EBGM scores for sedation ranged from 6.02 to 12.71 (median 7.58), and for antihistamines with low lipophilicity (cLogP<3)[#], EBGM ranged from 1.04 to 7.66 (median 2.53).

[#]Two known outliers (Loratadine and Rupatadine) were included in this category.

- Sedating antihistamines tended to have higher EBGM scores than non-sedating ones.
- For non-sedating beta-blockers EBGM scores ranged from 1.02 to 1.24 (median 1.13), for sedating beta-blockers EBGM ranged from 1.06 to 157.62 (median 1.66). Sedating beta-blockers tended to have higher EBGM scores than non-sedating ones.
- For NSAIDs with increased Cox-2 inhibition EBGM scores for MI ranged from 1.53 to 6.57 (median 4.92), for NSAIDs with lower Cox-2 inhibition EBGM scores ranged from 0.42 to 1.86 (median 0.78). NSAIDs with increased Cox-2 inhibition tended to have higher EBGM scores than NSAIDs with lower Cox-2 inhibition.

cLogP, calculated octanol/water partition coefficient; **cLogD**, calculated distribution coefficient (LogP at pH 7.4); **Cox-2**, cyclooxygenase-2.

Conclusions

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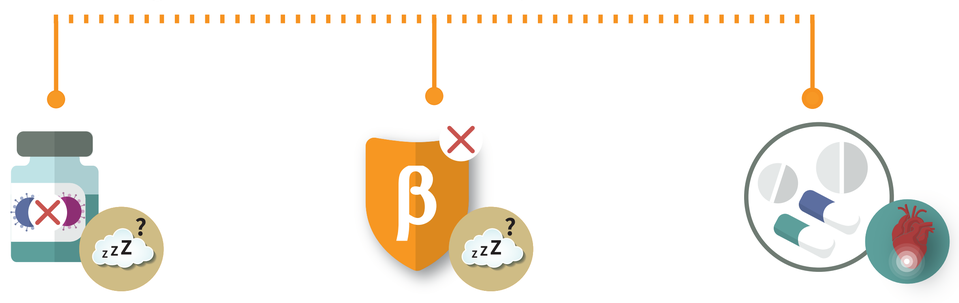
This correlation helps to differentiate insights for similar drugs.

- We used FDA safety data but these findings could generalize to healthcare databases.

Next-generation RWE

- should, when appropriate, consider the nature of exposures as continuous, multidimensional variables rather than binary inputs
- when combined with enriched clinical ontologies, could further unlock the potential of machine learning and artificial intelligence for pharmacovigillance by ensuring high volume of training data and minimizing information loss.

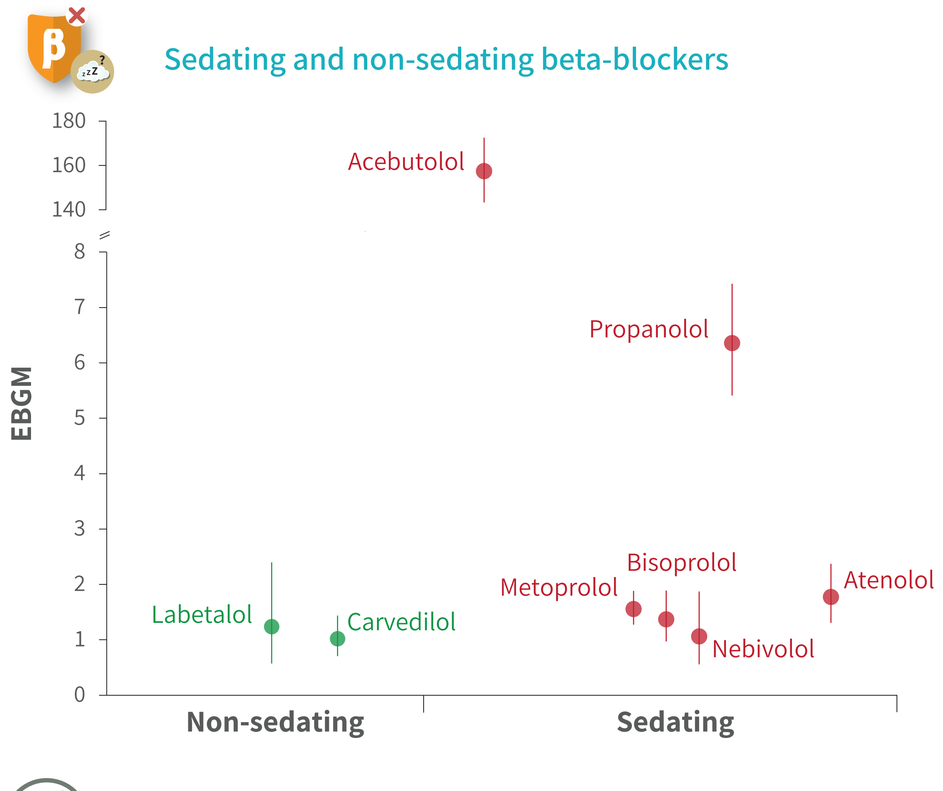
QSAR models were used, for:



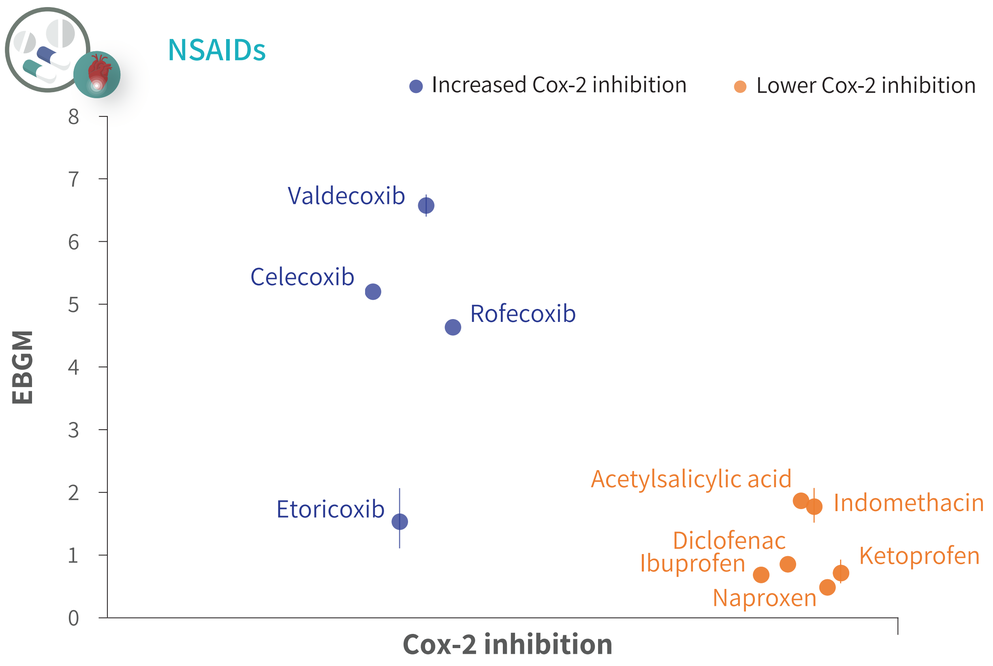
- Positive EBGM scores are predictive of safety signals. If the measure of disproportionality (EB05) is >2, there is a statistical alert[&] between drug and event.

NSAIDs, non-steroidal anti-inflammatory drugs. [&]A statistical alert requires further clinical review to determine if the criteria for a safety signal is met.

Sedating and non-sedating beta-blockers



NSAIDs



ISPOR Europe 2022, 6–9 November 2022, Vienna, Austria and Virtual

Funding: GlaxoSmithKline Biologicals SA. **Acknowledgments**: Medical writing (Lucia Adina Truta), design and coordination support were provided by Modis c/o GSK. **Disclosures**, **References**: available via the QR code.