

## QSPainRelief

Effective combinational treatment of chronic pain in individual patients, by an innovative quantitative systems pharmacology pain relief approach.

H2020 – 848068

### D 4.4: MVR and CUI public database

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## 1: Executive summary

The H2020 QSPainRelief project goal is to discover effective novel treatment combinations for pain relief and diminish side-effects in chronic pain patients. Within the QSPainRelief platform, predicted analgesic responses and side effects of the combinatory treatments were integrated into a Clinical Utility Index (CUI) model to predict which drug combinations are expected to benefit the patients the most.

A CUI model is a quantitative Benefit-Risk assessment framework where the side effects are weighted against the analgesic effect translating the responses in an overall clinical utility score. Using clinician informed weights of 1 for analgesia, 0.5 for sedation, 0.2 for cognitive impairment and 0.1 for drug abuse liability, the analgesic drug in combination with morphine that is predicted to benefit the patient the most is nortriptyline (CUI app\_v2025\_07v5).

When ranking the compounds by drug class and only looking at combinatory treatments, the drug class that is ranked first with a CUI score of 32.49 are Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) consisting of desvenlafaxine, duloxetine, milnacipran and venlafaxine. Whereas, with a CUI score of 25.92, Tricyclic antidepressants (TCAs) are ranked fourth consisting of amitriptyline, clomipramine, desipramine, doxepin, imipramine and nortriptyline.

## 2: Description of the Results for public dissemination

The results of a Clinical Utility Index (CUI) model (app\_v2025\_07v5) informed by the QSPainRelief model platform predicted data of endpoints representing analgesia, sedation, cognitive impairment and drug abuse liability, for compounds in combination with morphine, to see what drug combination would benefit chronic pain patients.

Using clinician informed weights of 1 for analgesia, 0.5 for sedation, 0.2 for cognitive impairment and 0.1 for drug abuse liability; the compound in combination with morphine that is predicted to benefit the patient the most is **nortriptyline**. So, this is the number one ranked combination compound. Other top contenders that are predicted to do well are (**unordered**):

- aripiprazole
- atomoxetine
- desvenlafaxine
- duloxetine

When grouping each drug according to the Anatomical Therapeutic Chemical (ATC) Classification the drug class that scores the best are\*:

	Ranking by drug class (top 4)	CUI score	Compounds within the class
1	Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	32.49	desvenlafaxine, duloxetine, milnacipran, venlafaxine
2	Norepinephrine Reuptake Inhibitor (NRI)	30.24	atomoxetine, reboxetine
3	Selective Serotonin Reuptake Inhibitors (SSRI)	29.91	citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
4	Tricyclic antidepressants (TCAs)	25.92	amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline

*\* Disclaimers: First of all, this is not medical advice. Second the model scores are derived from three predicted side effects. These do not encompass all the side effects that come with analgesics such as nausea, constipation, dry mouth, unintentional weight gain and even death due to respiratory arrest. And third, the modelled pathways also do not cover all mechanisms involved in analgesia, this also reflects in the selection of the compounds which is among others based on mode of action being present in the model.*

### 3: Summary

The H2020 QSPainRelief project goal is to discover effective novel treatment combinations for pain relief and diminish side-effects in chronic pain patients. Within the QSPainRelief platform, predicted analgesic responses and side effects of the combinatory treatments were integrated into a Clinical Utility Index (CUI) model (app\_v2025\_07v5) to predict which drug combinations are expected to benefit the patients the most. Using clinician informed weights of 1 for analgesia, 0.5 for sedation, 0.2 for cognitive impairment and 0.1 for drug abuse liability, the analgesic drug in combination with morphine that is predicted to benefit the patient the most is nortriptyline.