Title slide

Martens – Pre-Print Paper Presentation. I selected that title because it was a challenge to pronounce so many “P”s. But that is fitting as most antipsychotics are a challenge to pronounce.

Slide 1

Thanks for coming everyone. I chose this paper for several reasons and I look forward to hearing your impressions and comments on whether this new classification system is beneficial to our work.

This is a new work from the authors who are amongst the top 100 cited researchers in this field. Classification systems for these drugs is not new and these researchers have published previously on a classification system using network analysis.

Slide 2 – Background

So the focus of the paper is on developing a new classification system for AP medications. What is special about this work is that:

1. Strives to bridge the gap between clinical and research domains – and create a system that maps onto both pharmacological and clinical effects - the focus for clinicians may not be as strong on mechanisms, while a greater understanding of txt effects or side effects may provide researchers with insight or evidence of the mechanisms under study.
2. Create a classification system that facilitates a switch to another medication to improve txt response and tolerability.
3. Clarify oversimplification (typical/atypical, 1st vs 2nd gen.). These terms do not provide necessary information and simplifications obscure important similarities and differences between drugs. This group has actually a highly diverse pharmacology.

Slide 3 Method: Research-focused data

Step 1: Determine AP receptor affinities

- Receptor affinities obtained from NIMH. (Psychoactive Drug Screening Program database.)

- Include receptor if data were available for ≤ 5 separate drugs.

- Include AP if data were available for ≤ 5 separate receptors.

- Remove receptors if Ki values were identical for all drugs.

- Convert Ki to pKi values.

Slide 4 Method: Research-focused data

Step 2: Cluster APs by receptor affinities

- Adjusted the pKi values for agonists or partial agonists at a given receptor.

- Create correlation matrix with adjusted pKi values.

- Group AP with similar receptor profiles into distinct groups.

Slide 5 Method: Research-focused data

Step 3: Characterize relationships - receptor profiles, other classification methods, and clinical effects

- Performed Probabilistic PCA and calculated the average contribution of each cluster to the first three PCs. This is the mean component loading.(which explains the greatest proportion of variance).

- Compare the ability of these clusters to predict side effects.

- Compare results to existing methods of categorizing Aps including Neuroscience based Nomenclature, basic receptor profile defined groupings and the atypical/typical/partial agonist groupings.

- Evaluated median absolute error for 27 APs.

Slide 6 Method: Clinical-focused data

- Created a database of side effects as recorded in The Maudsley Prescribing Guidelines

- Data from meta-analyses RCT

- Compared effect size of side effect and AP to placebo

- Used National/International guidelines/consensus statements for missing side effects estimates.

- Normalized each side effect

Slide 7 Results: Clinical data 1: Antipsychotic pKi values

- 11 meta-analyses included out of 2060 meta-analyses

- 6 side effects available for ~22 APs. Marked with checks.

- Remaining derived from nat/int. guidelines, consensus statements

Slide 8 Results 1: Antipsychotic pKi values

- 27 APs and 42 receptors (AP on Y axis and Receptors on x axis)

- Larger pKi - greater affinity of the drug to the receptor

Slide 9 Results 2: AP correlation matrix

AP clustering based on receptor profiles. Stronger color indicates stronger correlation.

Slide 10 Results 3: Contribution of receptor-defined clusters to PCs

Amount of variation represented in PCs.

We have the 4 clusters on the left, in the middle, the bars show the mean loading or contribution of each cluster to the PCs.

They give an example that Cluster 4 has a large negative loading for PC1. Then on the right is a heatmap of how the PCs relate to the receptor profile.

The large negative loading for PC1 in cluster 4 indicates that the drugs in this cluster will tend to act as relatively strong antagonists at serotonin HTR1 and muscarinic receptor 1, and weak antagonists (or even agonists) at ADRA2B and ADRA2C.

Slide 11 Results 4: Characterized clinical profiles of PCs & receptor-defined clusters

In A, PCs on the Y axis and side effects on the x -axis. Red indicates that an AP that has a high contribution for that PC (from the previous figure) is likely to be associated with the effect.

In B, Clusters on the y axis and side effects on the x-axis. A darker color indicates that that cluster is sassociated with greater severity of the side effect in question (mean scores for AP clusters. From Fig2)

Slide 12 Results 5: Comparison of AP category methods & median error of clinical effects

1. In A we have a heat map comparing the different methods (typical/atypical/partial agonist, Neuroscience based Nomenclature, receptor-defined clusters (Fig 2) .
2. B shows the vertical lines on the x axis that are the abserved median error for predicting out of sample side effect profiles (a smaller value reflects more accurate prediction).

Slide 13. Conclusions

- Data-driven method provides a system for researchers and clinicians.

- ID of 4 groups of 42 receptors and 27 APs that map well to clinical profiles.

- Groups 1 and 4 were more efficacious than clusters 2 and 3.

- Method has potential for personalized psychiatry

predicting side effects

groups 1 & 4 more efficacious than 2 & 3