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 look forward to your impressions of this paper and a discussion of whether this new classification system is beneficial to our work.

Slide 2 – How I see it

The focus of the paper is on developing a new classification system for AP medications.

And it is also an attempt to bridge the gap between clinical and research domains – 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.

Knowledge gap: a data driven AP classification scheme suitable for cliniciansand researchers which maps onto both pharmacological and clinical effects. They want to fully understand the patterns of pharmacological similarity across compounds that may support initiatives to develop safer and more tolerable treatments. (According to ## researchers and clinicians need to agree about the definition of scz)

One often sees the terms “typical/atypical” or first/second generation in the literature. These terms do not provide necessary information as the compounds within the categories share neither common pharmacological or clinical profiles. In fact, there is a highly diverse pharmacology of this group of compounds. Simplifications obscures important similarities and differences between drugs.

Make a comment about their previous work with network analysis.

Slide 3

A classification system is needed that facilitates a switch to a second-line agent with a distinct pharmacological mechanism of action which may improved chances of txt response and/or tolerability.

In the interest of time, I thought we could focus on just four or five of the 27 AP discussed in the paper.

Method: Analysed affinities of 27 AP for 42 receptors from 3,325 receptor binding studies- covering a wide range of receptor types.These studies enable the construction of a receptor \*fingerprint\* for individual AP. So they synthesized the results of al relevant receptor binding studies to derive a receptor fingerprint for each AP. They apply an unbiased clustering algorithm to group AP with similar profiles, and then develop a ML model that uses receptor profieles to predict efficacy and side effect burden. (Step one addressed the needs of the researchers, and step two addressed the nees of the clinicials). Used a clustering algorithm to group AP based on their pattern of receptor affinity. They used a ML model to examine the ability of this grouping to predict AP-induced side effects quantified according to an umbrella review of clinical trial and txt guideline data.

Important point- the receptor-defined groupings show limited overlap with existing classification schemes but a good mapping to clinical profile, and by definition to receptor profiles.

(Convert Ki values to pKi values and reduce these values by 4 to produce a floor score of zero. - pki value multiplied by -1 for drugs was are agonists or partial agonists at a given receptor. This accounts for the functionally inverse effect.

A high correlation coefficient between 2 AP indicates that they share a similar receptor profile.

Slide 4 Results

Clustering resulted in four groups of antipsychotics. The predominant receptor affinity and effect/side effect ‘fingerprints’ of these four groups were defined, as follows: Group 1 - Muscarinic (M3-M5) receptor antagonism; Cholinergic and metabolic side effects. Group 2 - Dopamine (D2) partial agonism and adrenergic antagonism; Globally low side effect burden. Group 3 - Serotonergic and dopaminergic antagonism; Globally moderate side effect burden. Group 4 - Dopaminergic antagonism; Extrapyramidal and motor side effects. Groups 1 and 4 were more efficacious than clusters 2 and 3. The novel classification was superior to existing approaches when predicting side effects

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