Title Slide

Slide 2 Summer slide

I am going to present the final version of the project that is going in the manuscript – if the co-authors agree. Here the focus will be in the differentially methylated regions identified.

Slide 3 Aim: Identification of treatment effects

Olanzapine, quetiapine and risperidone – the drugs we are working with.

Our focus has always been on DNAm which has been shown to differ in individuals with severe mental illness compared to controls. And the differences are reported early – from prenatal into adolescence and across the last span. And increasingly there is evidence of the effect of antipsychotic drugs on DNA methylation not only in humans, but also in animals and cell lines.

Slide 4 Epigenetic modifications

While we study DNAm, we know that several epigenetic mechanisms work together. (Show where we are on the image.) We think of the association of DNAm on gene transcription, however, other enzymes contributing to changes in the tconformation of the chromatin (write more here).

Describe enzymes that demethylate or acetylate (readers and writers) That allow for differences in gene regulations

So, what I decided to do in this final part of the project was to look at the DMRs that we identified and see if there was a relationship to any of the other genes associated with epigenetic factors.

Slide 5. Sample Selection

I simplified the analysis by selecting the sample samples for each analysis – although we included the medication – free in the specific effects group to help with power.

Slide 6 Methods

Slide 7 Results: Common Effects

Slide 8 Results: Specific Effects

Slide 9 Database investigation of DMR genes

* SynGo

Slide 10 EpiFactors

Acknowledgements

So real-world observations studies are important to understand the long-term efficacy of AP. Usually these studies have longer follow-up periods compared to RCTs, and reflect a more accurate reflection of clinical practice. This is also a challenge as one study found that risperidone monotherapy had the highest txt discontinuation rate (TDR) and the shortest time to discontinuation (TTD), and olanzapine monotherapy was superior to polypharmacy in terms of long-term efficacy.

- Focus on response, rather than cross-sectional methylation status

- Real-world studies are also challenging - most are short term

- Median study duration 6 weeks, maximum 13 weeks (PMID:37159349)

- Treatment discontinuation rate (TDR) lower for monotherapy vs polypharmacy

- Risperidone highest TDR and shortest Time to discontinuation (TTD) (PMID:

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Slide 6