The clinical benefit of antipsychotic polypharmacy in refractory schizophrenia: a literature review

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Objective

Schizophrenia is a debilitating mental health disease that alters the way the affected person perceives reality. It involves a spectrum of symptoms, split into positive symptoms such as delusions and hallucinations, and negative symptoms, such as a blunted affect and poverty of speech and/or thought[1].

It was identified there is a gap between current mental health guidelines and clinical practice when using antipsychotic polypharmacy (AP) and treatment of resistant schizophrenia. International guidelines recommend the use of single agent therapy, whereas in practice, the majority of patients admitted to Mental Health Acute inpatient settings are prescribed AP.

A systematic quantitative literature review was conducted to review the potential benefits versus side effect burden of AP in the treatment of patients with refractory schizophrenia.

Method

Several databases were searched using primary search terms "Schizophrenia" and "Polypharmacy".

- 244 RCT's were searched
  - o **11** randomised controlled trials were reviewed.
- Nine trials utilised clozapine with a second generation antipsychotic (SGA)
- Two trials compared two SGAs.
- Changes in **Positive** and **Negative** symptoms were analysed
- Differences in **side effect burden** between polypharmacy and singe agent arms was reviewed.

Results

Table 1: Analysis of positive and negative symptoms in all trials included in the systematic review

		Positive Symptoms					Negative Symptoms					
Study	**Adjuvant Used**	**Assessment Tool**	**Within Group Difference***		**Between Group Difference+**		**Assessment Tool**	**Within Group Difference***		**Between Group Difference+**		**Side Effect**
			Value	**P**	**Value**	**P**		**Value**	**P**	**Value**	**P**	
Freudenreich O, 2007	Risperidone	PANSS	-0.9	-	-0.9	-	PANSS SANS	-1.2 -2.8	- -	-2.6 +0.6	- -	- VT (NS)
Honer O, 2006	Risperidone	PANSS	-3.0	<0.001	+2.0	-	PANSS	-3.1	<0.001	+1.1	-	-
Fleischhacker W, 2010	Aripiprazole	PANSS	-2.2	-	-0.3	-	PANSS	-1.9	-	+0.2	-	P <0.005 EPSE
Lee B, 2013	Aripiprazole	PANSS	-2.5	-	-11.6	<0.05	PANSS	-2.53	<0.05	-11.62	<0.05	-
Yasui-Furukori, 2012	Aripiprazole	PANSS	-2.1	-	+2.9	-	PANSS	-3.8	<0.001	-1.2	0.035	-
Muscatello M, 2014	Ziprasidone	PANSS	-0.3	-	+2.7	-	PANSS CDSS	-2.7 -1.3	0.001 0.018	-3.8 -1.1	0.006 -	- QT inc (NS)
Josiassen R, 2005	Risperidone	BPRS	-2.6	<0.001	-2.1	<0.05	SANS	-12.5	<0.04	-20.5	<0.05	-
Weiner E, 2010	Risperidone	BPRS	-2.6	-	-0.9	0.002	BPRS SANS	-1.5 -2.6	- -	-1.0 -3.1	0.002 -	Inc Prol
Muscatello M, 2010	Aripiprazole	SAPS	-6.4	0.002	-9.8	<0.001	SANS CDSS	-3.5 -2.1	- -	-9.8 -0.2	- -	-
Shiloh R, 1997	Sulpride	SAPS	-6.4	<0.05	-5.8	<0.05	PANSS HAM-D	-8.3 -2.7	<0.05 -	-6.8 -0.1	<0.05 -	Inc Prol
Fan X, 2013	Aripiprazole	-	-	-	-	-	-	-	-	-	-	-

*Comparison of results from trial initiation vs. end of trial
+Comparison of results from active group vs. placebo group

When we reviewed positive symptom improvement within the group, there were some isolated positive studies (N = 4 for cases with statistical significance), but not enough to demonstrate an overarching change. When comparing single agent to polypharmacy patient cohorts, 5 cases demonstrated statistical significance.

When we reviewed negative symptoms alone, there was further improvement in the within group and between group statistical significance (N = 7 and 6 respectively).

Table 2: Pooled results of tested side effects in active (polypharmacy) vs placebo (single agent) arms. A light green square indicates this side effect was not tested

		Metabolic Syndrome								
Study	**EPSE**	**Weight (kg)**	**Waist Circumference (cm)**	**Blood Glucose (mg/dl)**	**Cholesterol (mg/dl)**	**Triglycerides (mg/dl)**	**LDL (mg/dl)**	**Prolactin (µg/ml)**	**Neutrophil Count**	**Other reported side effects**
Freudenreich O, 2007										1 report of tachycardia (NS)
Honer O, 2006				+ 16.2 p=0.02				+69.8 p=<0.05		1 report of NMS (pt hx)
Fleischhacker W, 2010	9% inc	-2.53 P=<0.001	-2.0 p =0.001		-14.51 p=0.002	-12.6 p=0.003				Inc n&V, diarrhoea and anxiety
Lee B, 2013								-19.8 p=<0.001		NS UTI inc in Placebo
Yasui-Furukori, 2012	50% dec									-
Muscatello M, 2014										Sig inc in QT interval (nil clin outcomes)
Josiassen R, 2005										-
Weiner E, 2010								+32.5 p=0.001		NS inc in hypersalivation
Muscatello M, 2010										NS inc inmild transient sx
Shiloh R, 1997										-
Fan X, 2013								-151 p=0.019		NS inc in drowsiness, headache and hypersalivation

NS= Non-significant

Table 2 reviews the side effect burden of the AP arm compared to the single agent antipsychotic. This data was difficult to collate, as many studies utilised different markers of side effect burden, measured at different time points and usually for short periods of time. Two trials reported hyperprolactinemia and one case of elongated QT intervals, but this did not result in significant clinical outcomes.

Conclusion

This systematic review shows that AP for the treatment of refractory schizophrenia did not provide any additional benefit compared to single agent antipsychotic use. Studies looking at the augmentation of clozapine with ziprasidone, risperidone or sulpride showed promise for improving patients' symptom burden, particularly negative symptoms. Further trials would be needed to support these findings.

Positive symptoms associated with the disease state are usually the most distressing for the patient and people around them. It was therefore disappointing that the addition of a second antipsychotic did little to improve these symptoms.

The limitations of conducting studies in this population are important to note:

- It is very difficult to recruit in this cohort. A stable patient should not be changed off their current regime, making it difficult to find patients that are in the right phase of their treatment to recruit. Most studies were very small cohorts, meaning it is difficult to ensure statistical significance.
- Five of the 11 trials had stated conflict of interest with the drug companies manufacturing the medications studied.
- Many studies used different scoring scales for symptom control and side effect burden. Standardisation of psychiatric measuring scales should be implemented to allow the accurate comparison of data.

References

1. Organization WH. WHO | Schizophrenia [Internet]. Schizophrenia Fact Sheet. World Health Organization; 2014 [cited 2018 May 27]. Available from: http://www.who.int/mental_health/management/schizophrenia/en/

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