Identification of elevated and irritable subtypes in Bipolar I disorder in a treatment sample: What are the differences in treatment response?

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Introduction

In clinical practice and in the literature differing subtypes of bipolar disorder have been characterized. Greenwood et al (2013) identified clinical phenotypes associated with elated (elevated) and irritable subtypes. Others (e.g., Sato et al, 2002) have identified similar phenomenological subtypes and suggested that there are differences in treatment response.

This study (NCT01567527) used data from a randomized, double-blind, placebo-controlled trial to assess the time to recurrence of any mood episode in subjects with bipolar I disorder who have maintained stability on aripiprazole IM depot for at least 8 weeks. It was required at study entry that the patients were currently experiencing a manic episode with a YMRS score of ≥ 20. Because in this study the diagnostic criteria was for bipolar I disorder and had no specific indication of which DSMIVTR criteria were satisfied we were not able to determine irritable versus elevated subtype. We used the proxy of specific YMRS items to make the distinction.

It is important to understand potential treatment response differentials between subtypes to provide the best standard of care for patients that may have divergent symptom expressions even within the same diagnostic category. Both irritable and elevated subtypes can have serious clinical, social and sometimes legal consequences and clinicians should understand how a given compound works with their patients.

Objectives

To determine if there are differences in treatment response between elevated and irritable subtypes as compared to belonging to no subtype in an analysis of aripiprazole trial data using the YMRS scale.

Acknowledgment: This study was funded by Otsuka Pharmaceutical Development & Commercialization, Inc., and H. Lundbeck A/S

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Methods

Subjects included in the analysis were those that completed a screening visit and continued to the week 6 visit. All subjects in this phase of the trial were on oral aripiprazole and being cross titrated from their previous oral antipsychotic following a manic episode. The criteria for subgroup membership were the following:

Irritable Subtype: Irritability item score greater than 4 and Elevated Mood item score less than 3 at screening.

Elevated Mood Subtype**:** Elevated Mood item score greater than 2 and Irritability item score less than 4 at screening.

No subtype: All other YMRS item presentations.

These criteria are supported by factor analytic studies of the YMRS identifying subtypes and different factor structures (e.g., Hanwella & de Silva, 2011). The criteria are also supported by phenomenological subtypes identified in the literature (Sato et al., 2002). There is no precedent for the severity score cutoffs however, and this is based on the logic of the scale and severity score anchors.

Results

Using the design criteria we found that the elevated mood subtype at screening included 100 of 367 subjects (27% of the sample). Irritable mood subtype at screening included 40 subjects (11% of sample). There were 227 subjects (62%) that belonged to no subtype according to the analysis criteria.

There was a not a significant difference between YMRS total score rates of improvement (decrease in YMRS score) between these subtypes and with respect to belonging to no subtype.

Irritable subtype (n=40) μΔ screening to week 6 = 14.63

Elevated subtype (n=100) μΔ screening to week 6 = 15.64

No subtype (n=227) μΔ screening to week 6 = 15.88

A by-item analysis for each subtype (see Table 1) was conducted and in the irritable subtype there were very notable changes on the Irritability item (μΔ screening to week 6 = 3.30), the Speech (rate and amount) item (μΔ screening to week 6 = 2.35), the Content item (μΔ screening to week 6 = 2.16) as well as the Disruptive-Aggressive Behavior item (μΔ screening to week 6 = 2.30). The elevated mood subtype differences were more pronounced around the Elevated Mood item (μΔ screening to week 6 = 2.09) and Speech (rate and amount) item (μΔ screening to week 6 = 3.04). It is notable that the Elevated Mood item mean change from screening for the irritable subtype group was just .60 and the no subtype group was 1.44.

Table 1: YMRS item and total score effect sizes and mean change from screening to week 6 across subtypes.

Subtype	YMRS Item	Effect size	Cohen's d	Mean change
Elevated mood subtype	Elevated mood	0.8295	2.97	2.09
Elevated mood subtype	Increased motor activity	0.7209	2.08	1.73
Elevated mood subtype	Sexual interest	0.4749	1.08	1.32
Elevated mood subtype	Sleep	0.4633	1.05	1.3
Elevated mood subtype	Irritable mood	0.4408	0.98	1.08
Elevated mood subtype	Speech	0.7002	1.96	3.04
Elevated mood subtype	Language thought	0.6228	1.59	1.36
Elevated mood subtype	Content	0.4854	1.11	1.87
Elevated mood subtype	Disruptive/Aggressive	0.3939	0.85	0.97
Elevated mood subtype	appearance	0.3556	0.76	0.62
Elevated mood subtype	Insight	0.157	0.32	0.26
Elevated mood subtype	Total score	0.7929	2.6	15.64
Irritable subtype	Elevated mood	0.3398	0.72	0.6
Irritable subtype	Increased motor activity	0.433	0.96	1.05
Irritable subtype	Sexual interest	0.07	0.14	0.13
Irritable subtype	Sleep	0.4257	0.94	0.95
Irritable subtype	Irritable mood	0.7982	2.65	3.3
Irritable subtype	Speech	0.5332	1.27	2.35
Irritable subtype	Language thought	0.4062	0.89	0.77
Irritable subtype	Content	0.3393	0.87	2.16
Irritable subtype	Disruptive/Aggressive	0.6486	1.7	2.3
Irritable subtype	appearance	0.2965	0.62	0.55
Irritable subtype	Insight	0.2251	0.46	0.47
Irritable subtype	Total score	0.6967	1.94	14.63
No subtype	Elevated mood	0.6451	1.69	1.44
No subtype	Increased motor activity	0.6547	1.73	1.49
No subtype	Sexual interest	0.382	0.83	0.85
No subtype	Sleep	0.5876	1.45	1.41
No subtype	Irritable mood	0.6297	1.62	2.14
No subtype	Speech	0.6448	1.68	2.76
No subtype	Language thought	0.5994	1.5	1.15
No subtype	Content	0.4747	1.08	2.04
No subtype	Disruptive/Aggressive	0.5023	1.16	1.6
No subtype	appearance	0.3498	0.75	0.64
No subtype	Insight	0.1942	0.39	0.36
No subtype	Total score	0.7446	2.23	15.88

Conclusion

In the course of the trial we identified the presence of differing subtypes of bipolar disorder. We found that there were similar mean changes from screening to the week 6 visit as well as comparable effect sizes (see Table 1 above) in response to oral aripiprazole: this means that despite belonging to a given subtype, rates of response were similar. Clinically, this is important in deciding which medication may be appropriate for a given symptom presentation. The findings may have especially important implications for the treatment of the irritable subtype as these individuals are often considered more at risk and present different challenges in treatment.

References

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