

Adolescents with Psychotic Mania may Benefit from Maintenance Treatment with Adjunctive SGAs

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2009

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ABSTRACT

Background: Previously reported results from our placebo-controlled discontinuation study of adjunctive second generation antipsychotic medications (SGAs) in adolescents with Bipolar I Disorder included high rates of exacerbation of psychotic features or aggression, regardless of medication group assignment, and significant differences in weight trajectories between groups (1).

Methods: We examined whether the subgroup with psychotic features (n=11) differed from the subgroup with assaultive/destructive behavior (n=10) in time to clinically significant exacerbation using a Kaplan-Meier survival analysis. We also examined whether the differences in weight trajectory between the group that continued vs. discontinued adjunctive SGA treatment resulted in significant differences after 36 weeks of double-blind treatment in fasting glucose, insulin, triglycerides and total cholesterol using repeated measures analysis of variance (RMANOVA) with a mixed models approach.

Results: Rates of exacerbation during the 48-week double-blind period were nearly identical in the subgroups with aggression (7/10) and psychosis (8/11). However, remaining on active SGA resulted in a longer duration of stability relative to placebo (median 36 vs. 8 weeks) for the subgroup with psychotic features at entry but not for the subgroup with severe aggression but no psychosis (median 8 vs. 10 weeks). After 36 weeks of double-blind treatment (n=9) the group on placebo had lost weight, but the group on active treatment had gained slightly ($p < 0.046$). Both groups had significant declines over time in fasting glucose ($p < 0.042$) and triglyceride levels ($p < 0.027$). No changes over time were noted in insulin or total cholesterol levels.

Discussion: Our finding of high rates of recurrence across groups and weight loss following discontinuation of an SGA has also been reported in adults with bipolar disorder (2). Remaining on active SGA appeared to delay re-emergence of psychotic features in the subgroup of adolescents with psychosis at baseline but did not delay exacerbation in the subgroup receiving SGA for severe aggression. If replicated in a larger sample, this finding could have a significant impact on clinical practice by guiding the choice of long-term treatments on the basis of relevant clinical characteristics.

Figure 1: Study Design

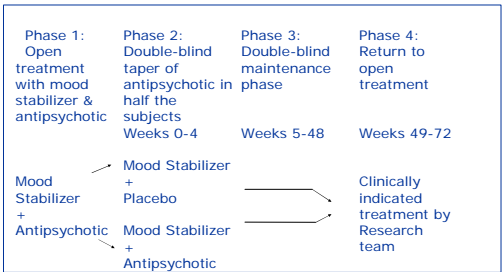
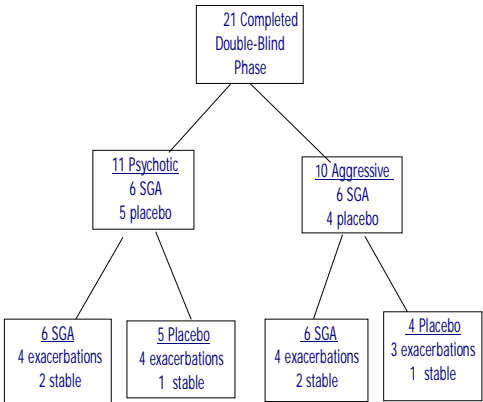
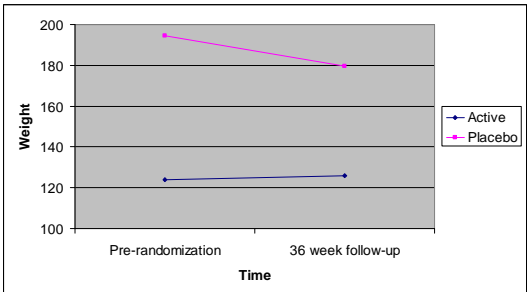


Figure 2: Subject Flow



Criteria for significant exacerbation consisted of a rating of mild on psychosis items such as Language-Thought Disorder and Content on the YMRS and Hallucinatory Behavior, Conceptual Disorganization, Suspiciousness and Grandiosity on the BPRS, or a rating of moderate on items measuring aggression.

Figure 3: Weight by Group Interaction at Pre-Randomization and 36-week follow-up (p<0.046)



RESULTS

Following combination treatment for at least 6 months with lithium and an SGA, 21 remitted subjects were randomly assigned to continue or discontinue their adjunctive SGA (See Figure 1). Of the 21 remitted subjects randomized, 11 had psychotic features and 10 had demonstrated severe aggression but no psychosis at study entry (see Figure 2). In this secondary analysis, we compared the outcomes of the psychotic (n=11) and non-psychotic (n=10) subgroups and examined longer-term weight and metabolic parameters. The psychotic and non-psychotic subgroups were similar in mean age at randomization (15.0 years and 14.4 years, respectively), had a comparable mean number of weeks in open treatment (34.11 weeks and 36 weeks, respectively) and did not differ significantly in gender or race. The subgroups also had similar numbers of participants on quetiapine, olanzapine, and risperidone as their SGA.

Although the proportions remaining stable during the 48-week double-blind period were similar between the groups, Kaplan-Meier survival analysis suggested that the psychotic subgroup had a longer duration of remission on SGA relative to placebo (median 36 vs. 8 weeks). In contrast, the non-psychotic subgroup had no change in the duration of remission when continuing SGA treatment vs. placebo (median 8 vs. 10 weeks).

Among subjects who continued in the double-blind portion of the study for at least 36 weeks (n=9), the group on placebo had lost weight, but the group on active treatment had gained slightly ($p < 0.046$; see Figure 3). Surprisingly, despite this difference in weight trajectory, both the active SGA and placebo groups had significant declines over time in fasting glucose ($p < 0.042$) and triglyceride levels ($p < 0.027$). No changes over time were noted in insulin or total cholesterol levels.

Our data suggest that continuing SGA treatment may prolong of psychotic mania but not non-psychotic mania. Despite ongoing weight gain in the group that continued SGA treatment, metabolic parameters appeared to improve over time, or at least not to worsen. A larger study limited to subjects with psychotic mania is warranted.

Tables 1 a and b: Outcome of Psychotic Mania During Double-Blind Phase

Psychotic Subgroup, Placebo Arm

ID	Weeks Stable in DB Phase	Exacerbation	Meds (mg/day) at Randomization	Meds (mg/day) at Study Term
59	3	Psychosis	QTP 600 LI 1125	QTP 600 LI 1125
17	6	Aggression	RSP 3.0 LI 1350 MPH-ER 72	VPA 1000 APZ 5.0 LI 1500 MPH-ER 72
1	8	Psychosis	VPA 1000 OLZ 20	VPA 1250 APZ 20.0
8	14	Psychosis	QTP 500mg LI 1125mg	QTP 500 LI 1350
44	48	N/A	QTP 300 LI 900	LI 900

Psychotic Subgroup, SGA Arm

ID	Weeks Stable in DB Phase	Exacerbation	Meds (mg/day) at Randomization	Meds (mg/day) at Study Term
41	11	Psychosis	FLX 10 OLZ 20 LI 1575	FLX 20 OLZ 10 LI 1350
32	20	Psychosis	Bup 300 OLZ 5 LI 900	OLZ 20 LI 1350
6	36	Withdrawn (disabling anxiety)	ETP 15 OLZ 10m LI 1350	OLZ 10 LI 1350
33	45	Psychosis	OXC 1200 QTP 500 LI 675	OXC 1200 QTP 400 LI 675
25	48	N/A	QTP 500 LI 900 VPA 1000	QTP 200 VPA 750 LI 675
35	48	N/A	OLZ 15 LI 1125	OLZ 15 LI 900

KEY: APZ: Aripiprazole Bup: Bupropion ETP: Escitalopram FLX: Fluoxetine LI: Lithium MPH: Methylphenidate OLZ: Olanzapine OXC: Oxcarbazepine QTP: Quetiapine
RSP: Risperidone VPA: Valproic Acid

References

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Funding Sources

Funding for this study was provided by NIMH grants R01 MH 60845 (PI: Kafantaris), M01 RR018535 (GCRC) and by an investigator initiated grant from Pfizer. Drug and matching placebo was provided by AstraZeneca, Eli Lilly & Co, Glaxo-Smith Kline, Janssen Pharmaceuticals and Pfizer.