“Knowing When a Drug is Not Going to Work in Bipolar Depression”: Absence of Early Improvement as a Predictor of Later Non-Response in 3,369 Patients From 10 Placebo-Controlled Acute Trials

Joseph R Calabrese,[1] David E Kemp,[1] Stephen J Ganocy,[1] Martin Brecher,[7] Berit X Carlson,[2] Suzanne Edwards,[9] James Eudicone,[2] Gary Evoniuk,[9] Wim T Jansen,[6] Robert McQuade,[3] Brian Millen,[8] Margaret Minkwitz,[7] Randall Owen,[5] Andrei Pikalov,[4] Armin Szegedi,[6] Mauricio Tohen,[8] Estelle Vester-Blokland,[2] Arjen PP van Willigenburg,[6]

[1]Case Western Reserve University, Cleveland, Ohio; [2]Bristol-Myers Squibb, Plainsboro, NJ; [3]Otsuka Pharmaceutical & Commercialization, Inc., Princeton, NJ; [4] Otsuka America Pharmaceutical, Rockville, MD; [5]Bristol-Meyers Squibb, Wallingford, CT; [6]Schering-Plough, Roseland, NJ; [7]AstraZeneca, Wilmington, DE; [8] Eli Lilly, Indianapolis, IN; [9]GlaxoSmithKline, RTP, NC.

Background: In testing for differences in depression symptom-severity between antidepressants and placebo in major depressive disorder (MDD) using repeated measures ANOVA, significant differences are usually not observed until week 3 (Everitt 1998, Montgomery 1995). Previously conducted pattern analyses have also posited that ‘true’ drug response does not occur until after 3 weeks (Quitkin et al 1987, 1993, 1996). Collectively, these findings have led to the belief that trials of antidepressants required 4-6 weeks of exposure, a practice which is difficult to operationalize and frequently encumbered by poor treatment adherence.

More recently, survival analytic techniques (Stassen et al 1993, 1996, 1999) have been applied to short-term randomized controlled trials in MDD and suggest that conditional probability of achieving response or remission in subjects experiencing early improvement is high. In fact, a meta-analysis of 47 double-blind, placebo-controlled antidepressant trials in MDD concluded that benefit was in fact occurring within the first 2 weeks of treatment (Posternak & Zimmerman, 2007).

These findings suggest that clinicians may be able to make rational treatment decisions in such patients after two weeks of treatment (Szegedi et al., 2003 & in press; Nierenberg et al., 1995). Since the predictive value of early improvement has never been studied in bipolar depression, similar analyses were undertaken in patients enrolled into 10 placebo-controlled, acute bipolar depression medication trials.

Methods: Ten similarly-designed, multicenter, randomized, double-blind, placebo-controlled trials in 3,369 patients with bipolar disorder experiencing major depression were blinded and used to determine if early improvement predicted later response and remission [2 aripiprazole studies (Thase et al., 2008), 5 lamotrigine (Calabrese et al., 2008), 1 olanzapine and olanzapine-fluoxetine combination (OFC) study (Tohen et al., 2003), and 2 quetiapine studies (Calabrese et al., 2005, Thase et al., 2006)]. 1,456 patients were randomized to placebo and 1,913 to active compounds.

Study designs and results are summarized in the following tables. Early improvement was defined as ≥ 20% reduction from baseline in MADRS total score at Week 2. Response was defined as ≥ 50% reduction in MADRS total score at endpoint (LOCF) [last observation carried forward] and CA [completer analyses]). Remission was defined as MADRS total score ≤ 10 at endpoint (LOCF&CA). Sensitivity, specificity, and positive (PPV) and negative predictive values (NPV) were calculated. Completer analyses yielded similar findings (data not shown). Weighted (shown) and unweighted analyses yielded similar results.

Predictive power analyses used LOCF, including 4 positive studies separating from placebo, the corresponding segregated placebo data, 6 negative/failed studies, and the corresponding segregated placebo data. Olanzapine and OFC data were pooled.

Summary of Randomized, Placebo-Controlled Trials in Bipolar I or II Depression

Drug and Author	Study Duration / Diagnostic Subtype	Number Randomized	% Responders / % Remitters	Reduction in MADRS (*P*)
Atypical Antipsychotic Monotherapy				
Aripiprazole Thase et al., 2008.	8 weeks BP I	ARP: 186 PBO: 188	ARP: 43.2 / 30.2 PBO: 39.0 / 27.8	*P*=NS
Aripiprazole Thase et al., 2008.	8 weeks BP I	ARP: 187 PBO: 188	ARP: 44.6 / 25.7 PBO: 44.3 / 29.0	*P*=NS
Olanzapine Tohen et al., 2003	8 weeks BP I	OLZ: 370 PBO: 377	OLZ: 39.0 / 32.8 PBO: 30.4 / 24.5	OLZ: 15.0 PBO: 11.9 (*P*=.002)
Quetiapine Calabrese et al., 2005	8 weeks BP I or II	QUE: 361 PBO: 181	QUE: 58.0 / 52.9 PBO: 36.1 / 28.4	QUE 600 mg/d: 16.73 QUE 300 mg/d: 16.39 PBO: 10.26 (*P*<.001)
Quetiapine Thase et al., 2006	8 weeks BP I or II	QUE: 341 PBO: 168	QUE: 59.2 / 52.0 PBO: 44.7 / 37.3	QUE 600 mg/d: 16.00 QUE 300 mg/d: 16.94 PBO: 11.93 (*P*<.001)
Anticonvulsant Monotherapy				
Lamotrigine Calabrese et al., 1999; Geddes et al, 2009.	7 weeks BP I (SCA2001)	LAM: 129 PBO: 66	LAM: 51.0 / NA PBO: 29.0 / NA	LAM 50 mg/d: 11.2 LAM 200 mg/d: 13.3 PBO: 7.8 (*P*<.05)
Lamotrigine Calabrese et al., 2008; Geddes et al, 2009.	10 weeks BP I or II (SCA2010)	LAM: 103 PBO: 103	LAM: 50.0 / NA PBO: 49.0 / NA	LAM: 12.0 PBO: 12.3 (*P*=NS)
Lamotrigine Calabrese et al., 2008; Geddes et al, 2009.	8 weeks BP I (SCA40910)	LAM: 133 PBO: 124	LAM: 46.0 / NA PBO: 39.3 / NA	LAM: 12.2 PBO: 11.2 (*P*=NS)
Lamotrigine Calabrese et al., 2008; Geddes et al, 2009.	8 weeks BP II (SCA100223)	LAM: 111 PBO: 110	LAM: 45.5 / NA PBO: 40.0 / NA	LAM: 13.4 PBO: 12.0 (*P*=NS)
Lamotrigine Calabrese et al., 2008	8 weeks BP I (SCA30924)	LAM: 131 PBO: 128	LAM: 54.1 / NA PBO: 45.7 / NA	LAM: 12.6 PBO: 11.7 (*P*=NS)
Combination Therapy				
Olanzapine-Fluoxetine Combination Tohen et al., 2003	8 weeks BP I	OFC: 86 OLA: 370 PBO: 377	OFC: 56.1 / 48.8 OLA: 39.0 / 32.8 PBO: 30.4 / 24.5	OFC: 18.5 OLA: 15.0 PBO: 11.9 (P=.002) (*P*<.001)

Results

1. 1,456 patients were randomized to placebo and 1,913 to active compounds in this 10 study analysis.
2. Negative predictive values were high (68-90%), suggesting the clinician can have high levels of confidence in knowing when a drug is not going to work in the acute treatment of bipolar depression.
3. Positive predictive values were low (38-73%), suggesting that the clinician never knows if a drug is going to work in the acute treatment of bipolar depression.
4. For studies that separated from placebo, false negatives were low for response (12-23%) and remission (11-19%).
5. For studies that separated from placebo, false positives were higher for response (28-58%) and remission (35-64%).

Discussion

1. If these trial data apply to clinical practice, medication change could be considered after 2 weeks of treatment in the absence of early improvement.
2. Efficacy, safety, and tolerability are important in drug development, but clinicians also value ‘predictability’, “knowing when a drug is going to work and knowing when it isn’t”.
3. Very Little research is devoted to the study of predictability of psychotropic drugs. Sponsors, regulators, and clinicians should consider this factor, especially in formulating evidence-based treatment guidelines.

Data provided by AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, and Otsuka.

Early Improvement as a Predictor of Later Response (Resp) or Remission (Rem) %		Sensitivity: True Positives / (True Positives + False Negatives)		Specificity: True Negatives / (True Negatives + False Positives)		Positive* Predictive Value: True Positives / (True Positives + False Positives)		Negative** Predictive Value: True Negatives / (True Negatives + False Negatives)		False Positives (1-specificity): If low, improvement reliably predicts response. If high, false sense of security.		False Negatives (1-sensitivity): If low, permits medication change early in the course of treatment. If high, causes needless worry.	
Arm	**Early Improvers**	**Resp.**	**Rem.**	**Resp.**	**Rem.**	**Resp.**	**Rem.**	**Resp.**	**Rem.**	**Resp.**	**Rem.**	**Resp.**	**Rem.**
Positive Studies													
Lamotrigine; Calabrese et al 1999. {1 study}	54	77	81	**69**	**65**	**73**	**62**	74	83	31	35	23	19
Olanzapine + Olanzapine/fluoxetine {1 study}	69	86	**88**	48	41	62	44	**77**	**86**	52	59	14	13
Quetiapine {2 studies}	75	88	**89**	42	36	68	54	**71**	**79**	58	64	12	11
Negative/Failed Studies													
Aripiprazole {2 studies}	68	81	**83**	43	41	54	44	**74**	**81**	57	59	19	17
Lamotrigine; Calabrese et al 2008. {4 studies}	44	63	63	**72**	**66**	**67**	**50**	68	76	28	34	37	37
Placebo Arms Pooled													
From 4 Positive Studies Total n = 703	54	80	81	**62**	**56**	**56**	**38**	83	90	38	44	20	19
From 6 Negative/Failed Studies Total n = 753	48	69	**70**	68	64	63	50	**74**	**80**	32	36	31	30

Yellow indicates a predictive power of relevance in clinical decision-making. * Confidence in knowing that the drug is working. ** Confidence in knowing that the drug is not going to work.*

Conclusions

1. Consistent with MDD, the absence of early improvement by day 14 during the acute treatment of bipolar depression predicts the absence of later response and remission.
2. High negative predictive values and low rates of false negatives suggest **high levels of confidence in knowing that response and remission is not going to occur;** Patterns of response for later non-improvers should be studied further.
3. High rates of false positives suggest that early improvement in patients who go on to exhibit non-response and non-remission is problematic and **gives the clinician and patients a ‘false sense of security’**.

Key References: 1. Stassen H, et al. Eur. Neuropsychopharmacol. 1993;3:127-35. 2. Stassen H, et al. Pharmacopsychiatry. 1996;29:87-96. 3. Stassen H, et al. Pharmacopsychiatry. 1999;32:56-60. 4. Stassen H, et al. J Clin Psychiatry. 2007;68:1195-1205. 5. Szegedi A, et al. J Clin Psychiatry 2003;64:413-20. 6. Szegedi A, et al. J Clin Psychiatry. In Press.