REVIEW ARTICLE

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When Do Psychiatric Patients Get Better? Timeline and Implications of Clinical Response to Treatment in Serious Mental Illness

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Abstract

One of the most important issues in clinical practice is determining if and when a treatment starts working and how long one should wait before reconsidering an unsuccessful medication trial. Prematurely switching an apparent early non-responder or maintaining an ineffective treatment for longer than necessary are two frequent and equally dangerous scenarios that can significantly prolong acute episodes and inflict additional undue suffering on patients. Finding the appropriate amount of time to wait for an improvement before pondering alterative therapeutic approaches is paramount in avoiding these pitfalls. While significant progress has been made in understanding the dynamics and implications of the response to psychotropic agents, there is still a lack of consensus regarding the application of these findings on a practical level. Most pharmacological studies use symptom scales to assess the effectiveness of a particular agent, but it is not always readily apparent how and when abstract variations in numerical score translate into concrete, visible improvements in disease severity. The aim of this review is to explore available data on the expected timeline of clinical response to treatment in patients with serious mental illness (schizophrenia, bipolar disorder, major depressive disorder) and its potential implications in optimizing clinical practice. Key points: i) Most exacerbations of schizophrenia show visible clinical improvement under neuroleptics within the first 14 days of treatment, and the absence of response at this point is highly predictive of further non-response, signaling the need for an alternative therapeutic approach, ii) Most manic episodes respond to treatment within 7 to 14 days and the absence of early improvement has been shown to be predictive of later non-response. However, a significant number of patients require longer periods to improve and the scope of available studies is relatively limited, iii) In bipolar depression the heterogeneity of therapeutic agents employed is mirrored in the varied patterns of response to treatment, iv) Most patients with unipolar depression who respond to antidepressants appear to exhibit clinical improvement within the first 14 days of treatment, with initial response being a good indicator for further response. However, because a substantial number of patients may respond slower, 4 weeks may be a more appropriate duration of time to wait before considering alternatives.

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INTRODUCTION

The last two decades have seen significant progress being made in understanding the timeline and dynamics of response to psychotropic agents. In schizophrenia, the paradigmatic shift was spearheaded by Agid et al. [1], who challenged the notion of the late onset of neuroleptic action, and culminated with the 2015 meta-analysis by Leucht et al. [2], which showed that a 2-week treatment course is sufficient to assess early non-response. Response to antidepressants in major depression has also been proven to be relatively rapid [3], with two separate meta-analyses [4,5] finding that treatment response at 2 weeks can be a reliable indicator for later improvement. On the other hand, high quality data on the timing of improvement in acute bipolar disorder remains surprisingly sparse, reflecting the heterogenous nature of symptoms and therapeutic agents.

However, there is still much uncharted territory as is reflected in the wide array recommendations offered by various treatment guides. The suggested duration for a course of antipsychotic medication varies from 2-4 weeks (American Psychiatric Association) [6] to 4 weeks (Canadian Guidelines) [7] to 4-6 weeks (National Institute

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for Health and Care Excellence) [8]. In bipolar disorder, the only recommendations regarding trial duration are found in Canadian Network for Mood and Anxiety Treatments / International Society for Bipolar Disorder guidelines [7], with 1-2 weeks being considered adequate for mania and 2 weeks for depressive episodes. In major depressive disorder, recommendations range from a minimum of 2-4 weeks (Canadian Network for Mood and Anxiety Treatments) [10] to 4-8 weeks (American Psychiatric Association) [9] to 4-6 weeks (Veterans Affairs/Department of Defense) [10] before considering alternative approaches. By examining the literature on which these guides draw upon, our review seeks to bring into focus the origins of these inconsistencies and to identify the areas that would most benefit from further investigation.

Schizophrenia

Agid et al [1] were the first to seriously challenge the hypothesis regarding the delayed action of antipsychotics. Their meta-analysis of 42 randomized controlled trials (RCT) found that response to neuroleptics (measured by percentual improvement of Positive and Negative Syndrome Scale/Brief Psychiatric Rating Scale (PANSS/BPRS) [13,14] scores compared to baseline) is significantly larger during weeks 1 and 2 of treatment compared to weeks 3 and 4. These findings also held true when assessing long-term response, with 70% of the total decline in PANSS/BPRS scores over 1 year of treatment taking place in the first 4 weeks [11]. Another meta-analysis [12] reconfirms this pattern of response for both first and second generation antipsychotics, with no significant differences between the two. There is also some evidence that improvement in treatment-resistant schizophrenia follows a similar course [13].

Leucht et al. [14] proved that patients who do not show any improvement during the first 2 weeks of treatment (0% BPRS reduction) are unlikely to respond by week 4 (defined here as less than 25% reduction in BPRS score). These results were further expanded to later endpoints (6 weeks) and with less stringent cut-off values [15]. Similar conclusions were drawn by Kinon et al [16], who also observed that early nonresponse (<20% decrease in PANSS at 2 weeks) can be reliably used to predict even later nonresponse (<40% decrease in PANSS at 3 months). Sensibility and positive predictive value (PPV) were relatively low (60% and 54% respectively), indicating that that early response does not necessarily predict a subsequent favorable outcome.

Perhaps the most important piece of the puzzle came into place with the pivotal meta-analysis of 34 studies [2] conducted by Leucht et al. Using the a priori definitions for early response as a 20% or more improvement of PANSS/BPRSS at 2 weeks of treatment and later response as 50% or more improvement of PANSS/BPRSS at endpoint, it concludes that absence of an early response predicts the absence of a later response in 90% of patients. It is noteworthy that by this point, the lack of predictive value of early improvement was a foregone conclusion.

While the data analyzed covered most antipsychotics and the majority of schizophrenia patients, these results could not be extended to two important subgroups: clozapine treated patients and first-episode patients. Although the meta-analysis did include studies of first-episode psychosis, these were relatively underrepresented (6 out of 34). While some support the 2 week rule, others suggest that longer trial periods might be more appropriate to separate responders from non-responders [21]. One study [17] found that as many as 55% of first-episode patients that achieve response (20% decrease in PANSS from baseline) only do so after the first two weeks.

Data regarding clozapine response is relatively sparse and heterogenous. A relatively large double blind trial found that most patients that improve (defined here as a decrease of at least 20% in BPRS scores) do so in the first 6 weeks and that about 27.1% of non-responders at 6 weeks attained later response [18]. A later meta-analysis seems to support the idea of a relatively rapid onset of clozapine response, with response curves flattening around 4-6 weeks [19].

To summarize, in acute episodes in chronically-ill schizophrenia patients, a lack of improvement after 2 weeks under optimal therapeutic doses is a reasonable predictor for the lack of later response, and may warrant a change in treatment. Those who do improve early are not guaranteed to remain responders at later points. First-episode psychosis and treatment-resistant schizophrenia, might have different patterns of short and long-term response [20]. Regarding Clozapine trials, minimal improvement can be expected as early as 4 to 6 weeks under appropriate doses, but a sizable subgroup of patients requires longer periods of time to respond.

Bipolar Disorder

Mania

The treatment of acute mania usually involves antipsychotics, mood stabilizers or a combination of the two. Two separate meta-analyses have shown neuroleptics to be superior to mood stabilizers in terms of efficacy, onset of effect and tolerability [26, 27]. However, even between neuroleptics, there is significant variation of these parameters, suggesting that their antimanic properties are not a “class effect” [22]. In clinical practice, manic patients often receive both an antipsychotic and a mood stabilizer, as there is compelling evidence that combined therapy is both more efficient and faster acting than monotherapy [29,30].

Considering the importance of the issue, there are few studies that investigate the parameters of antimanic response. A 2011 post-hoc analysis of Olanzapine and Risperidone treated patients (24) showed that early (1 week) non-improvement strongly predicted later lack of improvement or remission for both groups (negative predictive values – NPV range of 70-100%). The same conclusion was reached when comparing Olanzapine and Asenapine [25], with NPVs of 76% respectively 85%. A

naturalistic study of inpatients on various antimanic drugs, including combined therapy [26] suggests that assessing non-response at 1 week is not an adequate indicator of later outcomes, with predictive values being significantly higher after 2 weeks of treatment (NPV of 88% for response and 94.8% for remission at 4 weeks across all treatments). All of these defined early improvement as >25% decrease in Young Mania Rating Scale (YMRS) [27] score from baseline, later response as >50% decrease in YMRS score at endpoint, and remission as an YMRS score of 8 or less at endpoint. Endpoints were set at 3 or 4 weeks, with no subsequent follow-up.

However, trials that follow patients for longer periods of time (12 weeks) offer some important counterpoints. A 2005 RCT [28] comparing response rates to Quetiapine and Haloperidol found that while most responders did show improvement by week 3, a large portion of early non-responders (76.9% for Quetiapine and 64.3% for Haloperidol) went on to meet response criteria by the 12-week endpoint. Similar comparisons between Risperidone and Haloperidol [29] respectively olanzapine and haloperidol [30] also found significant numbers of late improvers. All three trials defined improvement as a 50% or more improvement of baseline YMRS score.

Another important consideration is that patterns of antimanic treatment response do not seem to be universal. By analyzing YMRS scores over 7 weeks, Lipkovich et al.[31] identified four distinct groups: early improvers that attain sustained remission (41.5%), partial responders (28.8%), early improvers that experience rapid relapse (16.2%) and early non-responders that later improve (13.5%).

The appropriate duration of time for an antimanic medication trial remains unclear. While short term studies evaluating nonresponse may suggest that 1 or 2 weeks might suffice, it is important to keep in mind that in longer trials, only about half to two-thirds of those who respond to treatment do so before week 3. Other important considerations are that the antimanic effect of neuroleptics seems to be more heterogenous than their effect on the symptoms of psychosis, that most studies assess response to monotherapy rather than combined treatment and that not all patients exhibit the same patterns of response.

Bipolar Depression

The pharmacotherapy of acute bipolar depression is a divisive issue. Antidepressant use is limited to adjunctive treatment in type I bipolar depression, and to patients with pure depressive symptoms in type II [32]. Amongst antipsychotics, quetiapine has consistently proven to be effective, with lurasidone, cariprazine and olanzapine (alone or in combination with Fluoxetine) also showing encouraging results. Other treatment options include lamotrigine, divalproex sodicum and lithium [7].

Considering the heterogenous nature of the agents used to treat bipolar depression, it is no surprise that the timing of response is not very clear. The only meta-analysis on this subject analyzed 10 positive and negative RCTs of both bipolar I and II patients. It reports that early improvement (defined as ≥20% reduction in Montgomery–Asberg Depression Rating Scale – MADRS [33] Total Score at Week 2) is not an accurate predictor of later response (defined as ≥50% reduction in baseline MADRS score at endpoint) and remission (defined as MADRS score ≤10 at endpoint). While sensitivity was 86/88% in pooled positive trials, false positives were frequent (53/59%). On the other hand, NPV was high (74/82%, with only 14/12% false negatives), suggesting that the absence of treatment response at 2 weeks may indicate a later lack of response. Positive trials included were for quetiapine [2], olanzapine + fluoxetine combination (OFC) [1] and lamotrigine [1, 34].

There are some individual considerations for the compounds included that may indicate the need for further research on this subject. A meta-analysis of Quetiapine trials shows that response patterns differ between bipolar I and bipolar II patients, with the latter showing slower initial improvement, but similar benefit at endpoint [35]. Additionally, the efficacity of Lamotrigine, in itself a point of debate, appears to be greater in more severely depressed patients [36] and slower in onset than that of OFC [37].

Another caveat is that the meta-analysis does not include trials of several drugs used in bipolar depression, notably lurasidone [38], cariprazine [39], and divalproex sodium [40]. While all of these are proven to have at least some efficiency, there are no studies that adequately address the dynamics of their therapeutic response. Lithium is another notable absentee, with surprisingly little quality evidence regarding its efficiency and timing of improvement considering its historical use [41]. Antidepressants are also omitted. It appears that acutely depressed type II patients have overall better and faster response and remission rates than type I and even unipolar depression patients, but rates of hypomanic switching were also higher (16% in bipolar II vs 9% in bipolar I) [42].

Given the variability of both intra – and interclass responses, non-equivalency between type I and type II bipolar depression and paucity of studies on the subject, it appears that there is no satisfactory response to the question of response timing at this moment.

Mixed States

There is very limited data on the treatment of acute mixed states. olanzapine, paliperidone and aripiprazole have some reasonable quality evidence for their efficacy in predominantly manic episodes. For episodes of predominantly depressive polarity, ziprasidone is the only agent that has shown some efficiency in an RCT. However, the scope of the results is limited, as the study only included BD-II patients. There is also some weak evidence for lurasidone, olanzapine and carbamazepine [43]. No studies regarding the timeline of response in mixed states have been found.

Major Depressive Disorder

Evidence of the relatively rapid effect of antidepressants has been found as far back as the 1960s [44]. However, it was not until 2005 that a meta-analysis was conducted on this subject [3]. Mirroring the findings regarding the rapid effects of neuroleptics, it reports that antidepressants have the greatest effect on symptoms of depression in the first two weeks of treatment, with 60.2% of the total improvement in Hamilton Depression Rating Scale (HDRS) [45] score taking place during this time. While this is also true for placebo treated patients, those treated with active drugs achieved symptom improvement more than twice as often, proving that the early effects of antidepressants are not placebo related [46].

The practical implications of this fact were assessed through another large meta-analysis, that found that if a patient did achieve some early improvement (defined as ≥20% score reduction from baseline in HDRS ratings at 14 days), later favorable outcomes were more likely. Conversely, early failure to respond to treatment strongly predicted later (28-42 days) lack of response. However, negative predictive values (82-100%) were significantly higher than positive predictive values (19-60%) [4].

Other authors examined different metrics for predicting the course of disease and found that when using a 29% improvement in QIDS-C (Quick Inventory of Depressive Symptoms) scores at 14 days as a benchmark for early improvement, PPV and NPV were roughly equal, at 70%. This means that, in contrast to using HDRS based cut-offs, it could reasonably predict both subsequent response and nonresponse [5].

A comparison of predictive value between individual classes of antidepressants shows that sensitivity and specificity do not significantly vary across categories, with the notable exception of serotonin reuptake inhibitors (SSRIs). Of the early non-improvers treated with SSRIs, about 1/3 attained later response or remission, compared to only 5-6% treated with mirtazapine or tricyclic's. Overall, early improvers were 8.37 times more likely to attain subsequent response and 6.38 times more likely to attain remission than non-responders [47].

On the other hand, a more recent study has concluded that, while patients who do not improve by week 2 had a relatively low chance to become responders by week 6 (17% for response, 13% for remission), the probability increases significantly by week 12 (39% for response and 26% for remission) [48]. There is also evidence that treatment-resistant patients do not exhibit the same patterns of response, and may require longer periods of time (4 weeks) to more accurately predict later outcomes [49].

In conclusion, while there is a substantial body of evidence that supports the hypothesis that antidepressants act rapidly and that the timeline of their effect is reasonably predictable, it is but one of many factors that a clinician should take into consideration when charting the course of optimal treatment.

Conclusion

The understanding of the dynamics of improvement under psychotropic agents has come a long way in the last 20 years. However, there is still much room for improvement. While some agents (antipsychotics, antidepressants) and disease entities are fairly well explored, others remain in need of further study, particularly bipolar disorder. An encouraging trend is seen in the efforts to find concrete, scale-based definitions for treatment response. High-quality large studies using commonly accepted metrics and specifically designed to address this issue would go a long way in developing better evidence-based guidelines.

REFERENCES

[1] Agid O, Kapur S, Arenovich T, Zipursky RB. Delayed-onset hypothesis of antipsychotic action. Arch Gen Psychiatry 2003;60(12):1228. doi:10.1001/archpsyc.60.12.1228.

[2] Samara MT, Leucht C, Leeflang MM, Anghelescu I-G, Chung Y-C, Crespo-Facorro B, et al. Early improvement as a predictor of later response to antipsychotics in schizophrenia: A diagnostic test review. Am J Psychiatry 2015;172(7):617–629. doi:10.1176/appi.ajp.2015.141.01329.

[3] Posternak MA, Zimmerman M. Is there a delay in the antidepressant effect? A meta-analysis. J Clin Psychiatry 2005;66(02):148–158. doi:10.4088/jcp.v66n0201.

[4] Szegedi A, Jansen WT, van Willigenburg APP, van der Meulen E, Stassen HH, Thase ME. Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder. J Clin Psychiatry 2009;70(3):344–353. doi:10.4088/jcp.07m03780.

[5] Gorwood P, Bayle F, Vaiva G, Courtet P, Corruble E, Llorca P-M. Is it worth assessing progress as early as week 2 to adapt antidepressive treatment strategy? Results from a study on agomelatine and a global meta-analysis. Eur Psychiatry 2013;28(6):362–371. doi: 10.1016/j.eurpsy.2012.11.004.

[6] National Institute for Health and Care Excellence (NICE). Psychosis and schizophrenia in adults: prevention and management Nice. 2014. https://www.nice.org.uk/guidance/cg178/resources/psychosis-and-schizophrenia-in-adults-prevention-and-management-pdf-351.097.58952133.

[7] Yatham LN, Kennedy SH, Parikh S V., Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018;20(2):97–170. doi:10.1111/bdi.12609.

[8] Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder. Can J Psychiatry 2016;61(9):540–560. doi:10.1177/070.674.3716659417.

[9] Gelenberg, A.J., Freeman, M.P., Markowitz, J.C., Rosenbaum, J.F., Thase, M.E., Trivedi MH, et al. American

Psychiatric Association practice guidelines for the treatment of patients with major depressive disorder. Arlington, VA: American Psychiatric Publishing, Inc.; 2010. http://www.psychiatryonline.com/pracGuide/pracGuideChapToc_7.aspx.

[10] DoD, VA. VA/DoD Clinical practice guideline for management of major depressive disorder (MDD). 2009. https://www.healthquality.va.gov/guidelines/MH/mdd/VADoDMDDCPGFINAL82916.pdf.

[11] Leucht S, Busch R, Hamann J, Kissling W, Kane JM. Early-onset hypothesis of antipsychotic drug action: a hypothesis tested, confirmed and extended. Biol Psychiatry 2005;57(12):1543–1549. doi: 10.1016/j.biopsych.2005.02.023.

[12] Sherwood M, Thornton AE, Honer WG. A meta-analysis of profile and time-course of symptom change in acute schizophrenia treated with atypical antipsychotics. Int J Neuropsychopharmacol 2006;9(03):357. doi:10.1017/S146.114.5705005961.

[13] Suzuki T, Remington G, Arenovich T, Uchida H, Agid O, Graff-Guerrero A, et al. Time course of improvement with antipsychotic medication in treatment-resistant schizophrenia. Br J Psychiatry 2011;199(4):275–280. doi: 10.1192/bjp.bp.110.083907.

[14] Leucht S, Busch R, Kissling W, Kane JM. Early prediction of antipsychotic nonresponse among patients with schizophrenia. J Clin Psychiatry 2007;68(03):352–360. doi:10.4088/jcp.v68n0301.

[15] Leucht S, Shamsi SAR, Busch R, Kissling W, Kane JM. Predicting antipsychotic drug response -replication and extension to six weeks in an international olanzapine study. Schizophr Res 2008;101(1–3):312–319. doi:10.1016/j.schres.2008.01.018.

[16] Kinon B, Chen L, Aschersvanum H, Stauffer V, Kollackwalker S, Sniadecki J, et al. Predicting response to atypical antipsychotics based on early response in the treatment of schizophrenia. Schizophr Res 2008;102(1-3):230–240. doi: 10.1016/j.schres.2008.02.021.

[17] Emsley R, Rabinowitz J, Medori R. Time course for antipsychotic treatment response in first-episode schizophrenia. Am J Psychiatry 2006;163(4):743–745. doi: 10.1176/ajp.2006.163.4.743.

[18] Rosenheck R, Evans D, Herz L, Cramer J, Xu W, Thomas J, et al. How long to wait for a response to clozapine: a comparison of time course of response to clozapine and conventional antipsychotic medication in refractory schizophrenia. Schizophr Bull 1999;25(4):709–719. doi:10.1016/j.schres.2008.02.021.

[19] Sherwood M, Thornton AE, Honer WG. A quantitative review of the profile and time course of symptom change in schizophrenia treated with clozapine. J Psychopharmacol 2012;26(9):1175–1184. doi: 10.1177/026.988.1112440513.

[20] Matei VP, Mihailescu AI, Davidson M. Is non-pharmacological treatment an option for certain schizophrenia patients? Psychiatr Danub 2014;26(4):308-313.

[21] Cipriani A, Barbui C, Salanti G, Rendell J, Brown R, Stockton S, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet 2011;378(9799):1306–1315. doi: 10.1016/S0140-6736(11)60873-8.

[22] Goikolea JM, Colom F, Capapey J, Torres I, Valenti M, Grande I, et al. Faster onset of antimanic action with haloperidol compared to second-generation antipsychotics. A meta-analysis of randomized clinical trials in acute mania. Eur Neuropsychopharmacol 2013;23(4):305–316. doi: 10.1016/j.euroneuro.2012.05.017.

[23] Ogawa Y, Tajika A, Takeshima N, Hayasaka Y, Furukawa TA. Mood stabilizers and antipsychotics for acute mania: a systematic review and meta-analysis of combination/augmentation therapy versus monotherapy. CNS Drugs 2014;28(11):989–1003. doi:10.1007/s40263.014.0197-8.

[24] Kemp DE, Johnson E, Wang W V, Tohen M, Calabrese JR. Clinical utility of early improvement to predict response or remission in acute mania. J Clin Psychiatry 2011;72(09):1236–1241. doi:10.4088/JCP.09m05874yel.

[25] Szegedi A, Zhao J, McIntyre RS. Early improvement as a predictor of acute treatment outcome in manic or mixed episodes in bipolar-1 disorder: A pooled, post hoc analysis from the asenapine development program. J Affect Disord 2013;150(3):745–752. doi:10.1016/j.jad.2013.01.024.

[26] Li D-J, Lin C-H, Lu M-J. Early improvement predicts treatment outcomes for patients with acute mania. J Clin Psychopharmacol 2017;37(4):435–440. doi:10.1097/JCP.000.000.0000000728.

[27] Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978;133(5):429–435. doi:10.1192/bjp.133.5.429.

[28] McIntyre RS, Brecher M, Paulsson B, Huizar K, Mullen J. Quetiapine or haloperidol as monotherapy for bipolar mania—a 12-week, double-blind, randomised, parallel-group, placebo-controlled trial. Eur Neuropsychopharmacol 2005;15(5):573–585. doi:10.1016/j.euroneuro.2005.02.006.

[29] Smulevich AB, Khanna S, Eerdekens M, Karcher K, Kramer M, Grossman F. Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol. Eur Neuropsychopharmacol 2005;15(1):75–84. doi:10.1016/j.euroneuro.2004.06.003.

[30] Tohen M, Goldberg JF, Gonzalez-Pinto Arrillaga AM, Azorin JM, Vieta E, Hardy-Bayle M-C, et al. A 12-week, double-blind comparison of olanzapine vs haloperidol in the treatment of acute mania. Arch Gen Psychiatry 2003;60(12):1218. doi:10.1001/archpsyc.60.12.1218.

[31] Lipkovich IA, Houston JP, Ahl J. Identifying patterns in treatment response profiles in acute bipolar mania: a cluster analysis approach. BMC Psychiatry 2008;8(1):65. doi:10.1186/1471-244X-8-65.

[32] Pacchiarotti I, Bond DJ, Baldessarini RJ, Nolen WA, Grunze H, Licht RW, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. Am J Psychiatry 2013;170(11):1249-1262. doi:10.1176/appi.ajp.2013.130.20185.

[33] Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134(4):382–389. doi:10.1192/bjp.134.4.382.

[34] Kemp DE, Ganocy SJ, Brecher M, Carlson BX, Edwards S, Eudicone JM, et al. Clinical value of early partial symptomatic improvement in the prediction of response and remission during short-term treatment trials in 3369 subjects with bipolar I or II depression. J Affect Disord 2011;130(1–2):171–179. doi:10.1016/j.jad.2010.10.026.

[35] Datto C, Pottorf WJ, Feeley L, LaPorte S, Liss C. Bipolar II compared with bipolar I disorder: baseline characteristics and treatment response to quetiapine in a pooled analysis of five placebo-controlled clinical trials of acute bipolar depression. Ann Gen Psychiatry 2016;15(1):9. doi:10.1186/s12991.016.0096-0.

[36] Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. Br J Psychiatry 2009;194(1):4–9. doi:10.1192/bjp.bp.107.048504.

[37] Brown EB, McElroy SL, Keck PE, Deldar A, Adams DH, Tohen M, et al. A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. J Clin Psychiatry 2006;67(07):1025–1033. doi:10.4088/jcp.v67n0703.

[38] Loebel A, Cucchiaro J, Silva R, Kroger H, Hsu J, Sarma K, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. Am J Psychiatry 2014;171(2):160–168. doi:10.1176/appi.ajp.2013.130.70984.

[39] Durgam S, Earley W, Lipschitz A, Guo H, Laszlovszky I, Németh G, et al. An 8-week randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in patients with bipolar I depression. Am J Psychiatry 2016;173(3):271–281. doi:10.1176/appi.ajp.2015.150.20164.

[40] Smith LA, Cornelius VR, Azorin JM, Perugi G, Vieta E, Young AH, et al. Valproate for the treatment of acute bipolar depression: systematic review and meta-analysis. J Affect Disord 2010;122(1–2):1–9. doi:10.1016/j.jad.2009.10.033.

[41] Zornberg GL, Pope HG. Treatment of depression in bipolar disorder. J Clin Psychopharmacol 1993;13(6):397-408.

[42] Tondo L, Baldessarini RJ, Vázquez G, Lepri B, Visioli C. Clinical responses to antidepressants among 1036 acutely depressed patients with bipolar or unipolar major affective disorders. Acta Psychiatr Scand 2013;127(5):355–364. doi:10.1111/acps.12023.

[43] Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Azorin J-M, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: acute and long-term treatment of mixed states in bipolar disorder. World J Biol Psychiatry 2018;19(1):2–58. doi:10.1080/15622.975.2017.1384850.

[44] Kammerer T, Singer L, Poirot JP. Amitryptiline in depressive states. Ann Med Psychol (Paris) 1963;121(1):440–447. [French]

[45] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23(1):56–62. doi:10.1136/jnnp.23.1.56.

[46] Papakostas GI, Perlis RH, Scalia MJ, Petersen TJ, Fava M. A meta-analysis of early sustained response rates between antidepressants and placebo for the treatment of major depressive disorder. J Clin Psychopharmacol 2006;26(1):56–60. doi:10.1097/01.jcp.000.019.5042.62724.76.

[47] Wagner S, Engel A, Engelmann J, Herzog D, Dreimüller N, Müller MB, et al. Early improvement as a resilience signal predicting later remission to antidepressant treatment in patients with major depressive disorder: systematic review and meta-analysis. J Psychiatr Res 2017;94:96-106. doi:10.1016/j.jpsychires.2017.07.003.

[48] de Vries YA, Roest AM, Bos EH, Burgerhof JGM, van Loo HM, de Jonge P. Predicting antidepressant response by monitoring early improvement of individual symptoms of depression: individual patient data meta-analysis. Br J Psychiatry 2019;214(1):4–10. doi:10.1192/bjp.2018.122.

[49] Olgiati P, Serretti A, Souery D, Dold M, Kasper S, Montgomery S, et al. Early improvement and response to antidepressant medications in adults with major depressive disorder. Meta-analysis and study of a sample with treatment-resistant depression. J Affect Disord 2018;227:777–786. doi:10.1016/j.jad.2017.11.004.