Psychiatr Q (2016) 87:305–313
DOI 10.1007/s11126-015-9388-9

ORIGINAL PAPER

Changing Trends in Treatment of Acute Mania: Experience of a Tertiary Centre Over a Decade

Mehmet Kemal Arıkan[1] · Cana Aksoy Poyraz[1] · Alper Baş[1] · N. Gamze Usta Sağlam[1] · Gizem Cetiner Batun[1] · Gözde Gültekin[1] · Burç Çağrı Poyraz[1]

Published online: 29 July 2015

Abstract We investigated trends over a decade in the prescription of lithium, antiepileptics, and antipsychotic agents at discharge for patients hospitalised for acute mania. We conducted a retrospective review of medical records for 165 inpatients with acute mania who had been hospitalised in Cerrahpaşa Faculty of Medicine, Department of Psychiatry during 2001–2002 and 2011–2012. Among 165 patients, prescription of olanzapine at discharge increased from 3 to 46 % ($p < 0.001$), while prescription of haloperidol decreased from 55 to 21 % ($p < 0.001$). Use of other atypical antipsychotics did not change significantly (risperidone decreased from 14 to 11 %, $p = 0.5$; quetiapine increased from 10 to 16 %, $p = 0.2$). Use of valproate, carbamazepine, and lithium did not change significantly. Use of electroconvulsive therapy in acute mania decreased by half from 27 to 13 % ($p = 0.02$). Typical antipsychotics alone or in combination with antiepileptics were the most common treatment regimen at discharge at 2001–2002; while 10 years later, they had been largely replaced by lithium or antiepileptics combined with second generation antipsychotics. Antipsychotic agents remained to be an important component of acute treatment of mania in our practice.

Keywords Bipolar disorder · Acute mania · Pharmacotherapy · ECT

✉ Cana Aksoy Poyraz
canaaksoy@yahoo.com

[1] Department of Psychiatry, Cerrahpaşa Faculty of Medicine, Cerrahpaşa Medical School, Istanbul University, Halaskargazi c. No:81 Çiçek apt. daire:8, Istanbul, Turkey

Introduction

Bipolar disorder (BD) is a severe and chronic illness. It is one of the leading causes of worldwide disability, especially in people aged 15–44 years [17]. Most patients experience recurring episodes at an average of 0.4–0.7 episodes per year, each lasting 3–6 months [1]. The beginning of a manic episode is sudden and acute hospitalization is often necessary. Controlling harmful behaviour to self and others, reducing suicide risk, providing acute sedation, and shortening the mood episode are amongst the reasons for hospitalisations [20].

Pharmacotherapy remains the mainstay of treatment for acute mania [24]. Pharmacological options for treatment of acute mania did not change significantly in recent decades, and lithium, valproate/divalproex, carbamazepine, and antipsychotics have long been the cornerstones of acute treatment for mania [11, 38]. In 1970s and 1980s, first-generation antipsychotics (FGAs) were considered short-term adjuncts for treatment of acute bipolar mania [14]. In the late 1990s, the second-generation antipsychotics (SGAs) olanzapine, risperidone and quetiapine emerged and were soon considered possible mood stabilizing agents [4, 12, 29]. SGAs overtook FGAs in the 2000s for the treatment of BD [18, 21, 33, 36, 37], and valproate became more popular than lithium by 2000s in some countries [3, 15, 18, 33, 36].

Evidence-based guidelines and decision algorithms have been developed to help clinical practitioners in the management of BD. However, patients in clinical practice may differ noticeably in terms of symptoms and treatment response from patients recruited for clinical trials [2]. Naturalistic prescription studies might detect differences between everyday clinical practice and evidence-based guidelines, and offer critical reflection on clinical treatment habits [36]. In light of these considerations, we sought to investigate the trends in treatment choices for patients hospitalised with severe acute mania over the last decade, focusing on our inpatient unit.

Methods

The study was approved by the Institute's Ethics Committee. We performed a retrospective review of the medical records of inpatients with acute mania who had been treated at the Department of Psychiatry, Cerrahpaşa School of Medicine, University of Istanbul, during 2001–2002 and 2011–2012.

At both periods, psychiatric diagnoses had been recorded according to the WHO International Classification of Diseases (ICD-10; [35]). Patients discharged with a primary diagnosis of either acute euphoric mania (ICD-10: F30.0-F30.9, F31.0-F31.2) or mixed-state/dysphoric mania (F31.6) were identified and selected for the current study. Demographics, characteristics of psychotropic drug prescription and adjunct use of electroconvulsive therapy (ECT) were compared for the first (2001–2002) and second (2011–2012) 2-year epochs.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 15. Analyses included χ^2 tests or Fisher's exact test as indicated for comparisons of categorical variables. Corresponding non-parametric tests were used when indicated. A two-tailed test of significance was used with an alpha level of $p = 0.05$.

Results

Demographics

In the first 2-year epoch (2001–2002), 78 patients (56.4 % female, 43.6 % male) with bipolar acute mania were admitted to the psychiatric inpatient unit. The average age of patients was 36.4 ± 12.1 years (range 18–73 years). In the second 2-year epoch (2011–2012), 87 bipolar patients (59.8 % female, 40.2 % male) were admitted, with an average age of 37.2 ± 14.4 years (range 16–70 years). Two samples were not significantly different in terms of gender and age characteristics. The number of days of hospitalisation did not differ significantly between the two periods (24.5 ± 12.6 days and 26.5 ± 14.2 days respectively; $z = -0.73$, $p = 0.46$).

Trends in Pharmacotherapy and ECT

Use of valproate, carbamazepine and lithium did not change significantly (Fig. 1). Frequency of olanzapine use increased from 3 to 46 % ($\chi^2 = 36$, df = 1, $p < 0.001$), while that of haloperidol decreased from 55 to 21 % ($\chi^2 = 18.1$, df = 1, $p < 0.001$) (Fig. 2). Use of other atypical antipsychotics did not change significantly. Risperidone decreased from 14.5 to 11.3 % ($\chi^2 = 0.35$, df = 1, $p = 0.5$), quetiapine increased from 10.1 to 16.3 % ($\chi^2 = 1.18$, df = 1, $p = 0.2$; see Fig. 2). Use of valproate, carbamazepine and lithium did not change significantly. Valproate decreased from 47.3 to 40.4 % ($\chi^2 = 0.51$, df = 1, $p = 0.4$), lithium decreased from 49.1 to 36.5 % ($\chi^2 = 1.71$, df = 1, $p = 0.19$), and carbamazepine increased from 20 to 26.9 % ($\chi^2 = 0.715$, df = 1, $p = 0.4$; see Fig. 1).Use of ECT in acute mania decreased by half from 26.9 to 12.6 % ($\chi^2 = 5.36$, df = 1, $p = 0.021$; see Fig. 2). Medical treatment regimens for the two groups at discharge were summarized in the Table 1. In the period between 2001–2002, typical antipsychotics

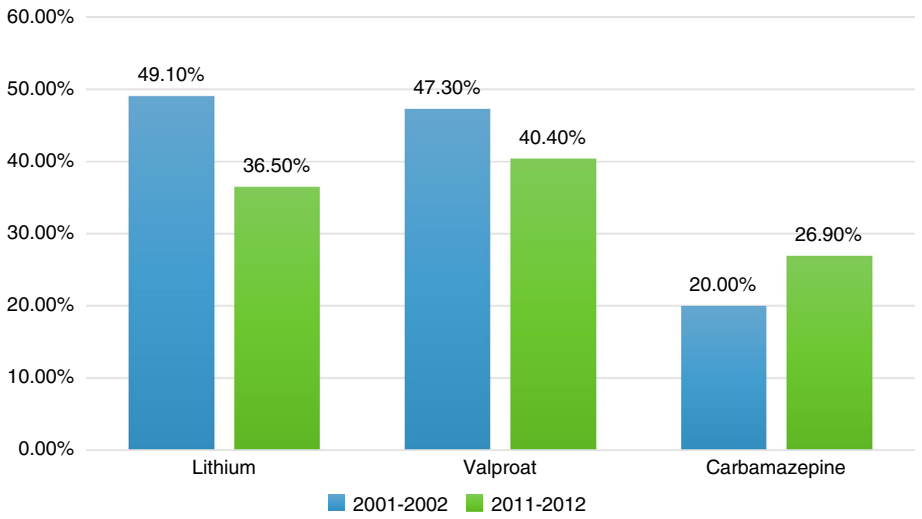

Fig. 1 Lithium, valproate, and carbamazepine usage trends in patients hospitalised with acute mania during 2001–2002 and 2011–2012. Use of valproate, carbamazepine, and lithium did not change significantly

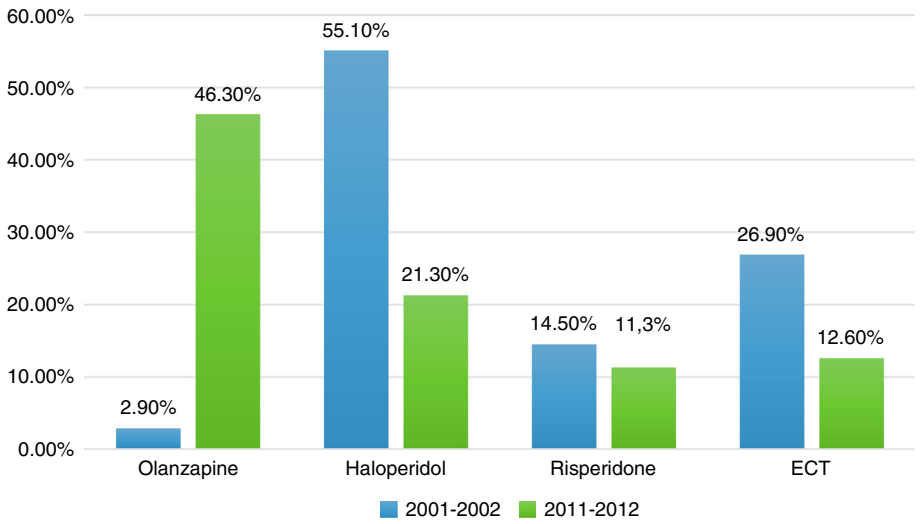

Fig. 2 Olanzapine, risperidone, haloperidol, and ECT usage trends in patients hospitalised with acute mania during 2001–2002 and 2011–2012. Olanzapine usage increased significantly ($p < 0.001$), and haloperidol use decreased significantly ($p < 0.001$). Risperidone use did not change significantly ($p = 0.5$). Use of ECT in acute mania decreased by half ($p = 0.02$)

Table 1 Treatment regimens at discharge for patients hospitalised with acute mania between 2001 and 2002 or 2011 and 2012

	2001–2002		2011–2012		Statistics		
	n = 78	%	n = 87	%	χ^2	df	*p*
Lithium + atypical AP	5	7	14	16	3.77	1	0.05
Lithium + typical AP	10	13	0	0			<0.001[a]
Typical AP	18	23	7	8	7.26	1	0.007
Atypical AP	2	3	18	21	12.68	1	<0.001
Valproate/carbamazepine + atypical AP	10	13	30	35	10.51	1	0.001
Lithium monotherapy	4	5	4	5			1[a]
Valproate/carbamazepine	4	5	0	0			0.04[a]
Valproate + carbamazepine	1	1	0	0			0.47
Lithium + AE	4	5	0	0			0.04[a]
Lithium + AAP/AP + AE	2	3	1	1			0.60[a]
Valproate/carbamazepine + typical AP	18	23	3	4		14.31	<0.001
Typical AP + atypical AP	0	0	9	11			0.003[a]

The groups were compared with χ^2 tests unless otherwise specified

AE antiepileptics, *AP* antipsychotics, *AAP* atypical antipsychotics

[a] Groups were compared with Fisher's exact test

as monotherapy and in combination with antiepileptics (AEs) were the most common treatment regimen at discharge (23 %). On the other hand, AEs (valproate/carbamazepine) combined with atypical antipsychotics were the predominant treatment choice in the period

between 2011–2012 (35 %), followed by monotherapy with atypical antipsychotics (21 %), while the combination of lithium and atypical antipsychotics was the third choice (16 %). Lithium and AEs, as monotherapy or in combination, were not preferred during either period.

Discussion

We found that clinicians' choice of treatment for patients hospitalised with acute mania had changed significantly over the first decade of 2000's. The prescription of haloperidol at discharge diminished, whereas that of olanzapine increased markedly over this period, possibly reflecting the preference of clinicians for the maintenance phase of BD. In our clinical practice, typical antipsychotics as monotherapy and in combination with AEs were the most common treatment regimens at discharge in the early 2000s. Ten years later, these had been largely replaced by AEs (valproate/carbamazepine) combined with atypical antipsychotics or atypical antipsychotics alone. The combination of lithium and typical antipsychotics dropped almost completely, while the combination of lithium and atypical antipsychotics became the third most frequent choice in 2011–2012. These trends indicate that antipsychotics remained to be an important part of treatment for acute mania, either alone or in combination with mood stabilizers. We also found that while use of typical antipsychotics (particularly haloperidol) was still predominant in the early 2000s, use of olanzapine had overtaken these agents by 2011. Prescription rates of AE's and lithium did not change significantly over the decade; however, the combination of lithium and atypical antipsychotics rose significantly.

The major treatment of choice found in the current study (considering antipsychotics as primary therapy, either alone or in combination with mood stabilizers) was consistent with several prior reports from other settings. For instance, the most common pattern of pharmacological treatment for an acute manic or mixed episode in China was found to be a mood stabilizer in combination with an atypical antipsychotic (N = 1345, 47.6 %; [34]), which confirmed that polypharmacy for acute manic episodes was a common phenomenon [36]. Furthermore, evidence from both clinical practice and randomized control trials showed that addition of antipsychotics to lithium or valproate was superior to lithium or valproate alone, however there was limited evidence to support this combination as a general first-line treatment [19]. Despite the heterogeneity of studies related to differences in methodology, most studies reported a major effect of combined treatments compared to mood stabilizer monotherapies in the treatment of acute mania [6]. In a recently published meta-analysis including 19 randomized control trials, a mood stabilizer plus antipsychotic combination/augmentation therapy was found to be more effective than mood stabilizer monotherapy in terms of the change in mania rating scale scores at 3 weeks. However, the combination/augmentation therapy was associated with more side effects, primarily somnolence [28]. Another systematic review encompassing 1124 patients showed that atypical antipsychotic co-therapy significantly reduced manic symptoms compared to mood stabilizer monotherapy [31].

With regard to the choice among SGAs, we found that olanzapine use increased dramatically over the studied period (from 3 to 46 %). Contrary to our findings, olanzapine use seems to have decreased in many inpatient settings [8, 18, 33]. Olanzapine use increased, however in one prior study that investigated prescribing patterns for BD in primary care [21].

Preferring olanzapine to risperidone does not seem to be a choice related to efficacy, as risperidone has been found equally effective in the control of manic episodes [9]. A multiple treatment meta-analysis showed that overall, antipsychotic drugs were significantly more effective than mood stabilizers in the management of acute mania; the authors found that risperidone, olanzapine, and haloperidol were among the best of the available options for the treatment of manic episodes [9], which is well reflected in our clinical practice. Although olanzapine has a significantly adverse metabolic profile, its efficacy in controlling manic episodes, in addition to a better extrapyramidal symptoms profile might have contributed to the choice of olanzapine in our setting. The high risk of extrapyramidal side effects associated with risperidone [32] and the connection between extrapyramidal side effects and treatment-emergent depression in continuing care might be the factors in favour of choosing olanzapine. On the other hand, combination therapy with SGAs and lithium/AEs at discharge might be due to the concern that SGAs alone would not be strong enough to prevent relapses. In a review article that assessed the effects of olanzapine in preventing manic, depressive, and mixed episodes in patients with bipolar affective disorder, the authors found that in the long-term olanzapine was associated with a lower rate of manic episodes, but a higher rate of weight increase and depression compared to lithium [10].

The dramatic decrease in use of haloperidol was likely connected with a perceived higher risk of depression and extrapyramidal symptoms with this agent compared to SGAs [13]. In parallel with our findings, another study conducted in Germany that compared drug prescriptions for acute mania from 1994–2004 found that the administration of atypical antipsychotics more than doubled, while the use of typical antipsychotics decreased significantly [36]. Though we report relatively high prescription rates for conventional antipsychotics in our sample at early 2000s, it should be noted that these agents might have been used preferentially for a rapid control of manic symptoms. Although discontinuation of antipsychotics some weeks after the symptom control is generally recommended, it has been reported in other settings that patients are often not tapered off of their medication after discharge from the hospital [30].

Our data contrasts with that of prior studies suggesting a dramatic increase in valproate use in the 2000s compared to lithium for patients with acute mania [33, 36]. In a large sample of patients with BD in the United Kingdom over a 15-year period, the authors found that lithium use remained relatively constant, while the use of SGAs and valproate increased dramatically [21]. In contrast, we observed a non-significant decrease in valproate use in our practice.

In a recent study, the authors investigated trends in prescription rates from 2000–2011 in outpatients with bipolar I disorder and bipolar II disorder referred to a BD specialty clinic. They found that use of lamotrigine, quetiapine, and aripiprazole increased more than twice while olanzapine and risperidone use decreased by more than half [22]. The side effect profiles of olanzapine and risperidone (weight gain and extrapyramidal side effects, respectively) may have contributed to these results. In addition, syndromal/subsyndromal depression was found in 37 % of the sample. This is a high figure, suggesting that in order to treat subsyndromal depression (a serious, unresolved problem also responsible for social disability in BD; [5]), clinicians prefer lamotrigine, quetiapine, and aripiprazole, all of which have antidepressant properties and are used for the prevention or acute treatment of depression [7, 16, 23].

Finally, the use of ECT in acute mania in our sample decreased by half, from 27 to 13 %. Long-term stabilization of BD is a major challenge, and this decline in ECT practice might be related to high relapse rates in the early months after ECT [25]. Evidence

indicates that ECT is associated with remission or marked clinical improvement in up to 80 % of manic patients [27], and may be considered at any point as treatment for acute mania if the patient has a history of positive response or is intolerant of medications [26]. This trend in ECT might also be related to alterations in haloperidol prescription rates, since treating acute mania with haloperidol might be associated with higher risks of depression and extrapyramidal symptoms compared to SGAs [13]. This might explain, at least in part the higher need for ECT in the first epoch of our sample.

This study has several limitations. Since our study was cross-sectional and retrospective, the role of combination therapy during the course of an acute episode was unknown. No validated instrument was used to assess diagnosis. Information about the basis for the prescribing decision was not obtained. Due to sampling from a single institution, these findings may not reflect the diversity seen in clinical practice.

Conclusions

Over 10 years (2001–2002 to 2011–2012), the use of haloperidol for treatment of acute mania at hospital discharge has been widely discontinued, whereas we observed a significant increase in prescription of olanzapine. This trend indicates that olanzapine was effective for the acute control of symptoms and was favoured by clinicians for continuing care. Typical antipsychotics as monotherapy or combined with AE were the most common treatment regimen at discharge in the early 2000s, whereas 10 years later they were largely replaced by lithium or AE combined with SGA. However, antipsychotics as a primary therapy and in combination with mood stabilizers remained the first choice for acute mania. Use of ECT in acute mania decreased by half over 10 years.

Acknowledgments This research received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

Compliance with Ethical Standards

Conflict of interest The authors declare that there is no conflict of interest.

References

1. Angst J, Sellaro R: Historical perspectives and natural history of bipolar disorder. Biological Psychiatry 48:445–57, 2000.
2. Baldessarini RJ: Treatment research in bipolar disorder: issues and recommendations. CNS Drugs 16:721–9, 2002.
3. Baldessarini RJ, Leahy L, Arcona S, Gause D, Zhang W, Hennen J: Patterns of psychotropic drug prescription for U.S. patients with diagnoses of bipolar disorders. Psychiatric Services 58:85–91, 2007.
4. Berk M, Ichim L, Brook S: Olanzapine compared to lithium in mania: a double-blind randomized controlled trial. International Clinical Psychopharmacology 14:339–343, 1999.
5. Bonnin CM, Martinez-Aran A, Torrent C, Pacchiarotti I, Rosa AR, Franco C, Murru A, Sanchez-Moreno J, Vieta E: Clinical and neurocognitive predictors of functional outcome in bipolar euthymic patients: a long-term, follow-up study. Journal of Affective Disorders 121:156–160, 2010.
6. Buoli M, Serati M, Altamura AC: Is the combination of a mood stabilizer plus an antipsychotic more effective than mono-therapies in long-term treatment of bipolar disorder? A systematic review. Journal of Affective Disorders 152–154:12–18, 2014.
7. Calabrese JR, Keck PE Jr, Macfadden W, Minkwitz M, Ketter TA, Weisler RH, Cutler AJ, McCoyR, WilsonE, Mullen J: A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. American Journal of Psychiatry 162:1351–1360, 2005.

8. Centorrino F, Ventriglio A, Vincenti A, Talamo A, Baldessarini RJ: Changes in medication practices for hospitalized psychiatric patients: 2009 versus 2004. Human Psychopharmacology 25:179–186, 2010.
9. Cipriani A, Barbui C, Salanti G, Rendell J, Brown R, Stockton S, Purgato M, Spineli LM, Goodwin GM, Geddes JR: Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet 378:1306–15, 2011.
10. Cipriani A, Rendell J, Geddes JR: Olanzapine in the long-term treatment of bipolar disorder: a systematic review and meta-analysis. Journal of Psychopharmacology 24:1729–1738, 2010.
11. Geddes JR, Miklowitz DJ: Treatment of bipolar disorder. Lancet 381:1672–1682, 2013.
12. Ghaemi SN, Katzow JJ: The use of quetiapine for treatment-resistant bipolar disorder: a case series. Annals of Clinical Psychiatry 11:137–140, 1999.
13. Goikolea JM, Colom F, Torres I, Capapey J, Valenti M, Undurraga J, Grande I, Sanchez-Moreno J, Vieta E: Lower rate of depressive switch following antimanic treatment with second-generation antipsychotics versus haloperidol. Journal of Affective Disorders 144:191–198, 2013.
14. Goodwin FK: Manic-depressive illness. Oxford University Press, New York, 1990.
15. Goodwin FK, Fireman B, Simon GE, Hunkeler EM, Lee J, Revicki D: Suicide risk in bipolar disorder during treatment with lithium and divalproex. Journal of the American Medical Association 290:1467–1473, 2003.
16. Goodwin GM, Bowden CL, Calabrese JR, Grunze H, Kasper S, White R, Greene P, Leadbetter R: A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. Journal of Clinical Psychiatry 65:432–41, 2004.
17. Goodwin GM; Consensus Group of the British Association for Psychopharmacology: Evidence-based guidelines for treating bipolar disorder: revised second edition—recommendations from the British Association for Psychopharmacology. Journal of Psychopharmacology 23:346–88, 2009.
18. Greil W, Haberle A, Haueis P, Grohmann R, Russmann S: Pharmacotherapeutic trends in 2231 psychiatric inpatients with bipolar depression from the International AMSP Project between 1994 and 2009. Journal of Affective Disorders 136:534–42, 2012.
19. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moller HJ, Kasper S.: The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. World Journal of Biological Psychiatry 10:85–116, 2009.
20. Harris EC, Barraclough B: Suicide as an outcome for mental disorders. A meta-analysis. British Journal of Psychiatry 170:205–228, 1997.
21. Hayes J, Prah P, Nazareth I, King M, Walters K, Petersen I, Osborn D: Prescribing trends in bipolar disorder: cohort study in the United Kingdom THIN primary care database 1995–2009. PLoS ONE 6:e28725, 2011.
22. Hooshmand F., Miller S, Dore J, Wang PW, Hill SJ, Portillo N, Ketter TA: Trends in pharmacotherapy in patients referred to a bipolar specialty clinic, 2000-2011. Journal of Affective Disorders 155:283–287, 2014.
23. Malempati RN: Aripiprazole adjunct treatment in bipolar I or II disorder, depressed state: a 2-year clinical study. Journal of Nervous and Mental Disease 203:58–64, 2015.
24. McElroy SL, Keck PE Jr: Pharmacologic agents for the treatment of acute bipolar mania. Biological Psychiatry 48:539–57, 2000.
25. Medda P, Toni C, Perugi G: The mood-stabilizing effects of electroconvulsive therapy. Journal of ECT 30:275–82, 2014.
26. Mohammad O, Osser DN: The psychopharmacology algorithm project at the Harvard South Shore Program: an algorithm for acute mania. Harvard Review of Psychiatry 22:274–294, 2014.
27. Mukherjee S, Sackeim HA, Schnur DB: Electroconvulsive therapy of acute manic episodes: a review of 50 years' experience. The American Journal of Psychiatry 151:169–176, 1994.
28. 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 28: 989–1003, 2014.
29. Segal J, Berk M, Brook S: Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial. Clinical Neuropharmacology 21:176–180, 1998.
30. Sernyak MJ, Griffin RA, Johnson RM, Pearsall HR, Wexler BE, Woods SW: Neuroleptic exposure following inpatient treatment of acute mania with lithium and neuroleptic. American Journal of Psychiatry 151:133–135, 1994.
31. Smith LA, Cornelius V, Warnock A, Tacchi MJ, Taylor D: Acute bipolar mania: a systematic review and meta-analysis of co-therapy vs. monotherapy. Acta Psychiatrica Scandinavica 115:12–20, 2007.
32. Srivastava S, Ketter TA, Clinical relevance of treatments for acute bipolar disorder: balancing therapeutic and adverse effects. Clinical Therapeutics 33:B40–B48, 2011.

33. Walpoth-Niederwanger M, Kemmler G, Grunze H, Weiss U, Hortnagl C, Strauss R, Blasko I, Hausmann A: Treatment patterns in inpatients with bipolar disorder at a psychiatric university hospital over a 9-year period: focus on mood stabilizers. International Clinical Psychopharmacology 27:256–266, 2012.
34. Wang Z, Gao K, Hong W, Xing M, Wu Z, Chen J, Zhang C, Yuan C, Huang J, Peng D, Wang Y, Lu W, Yi Z, Yu X, Zhao J, Fang Y: Pharmacotherapy for acute mania and disconcordance with treatment guidelines: bipolar mania pathway survey (BIPAS) in mainland China. BMC Psychiatry 14:167, 2014.
35. WHO: The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva, World Health Organization, 1992.
36. Wolfsperger M, Greil W, Rossler W, Grohmann R: Pharmacological treatment of acute mania in psychiatric in-patients between 1994 and 2004. Journal of Affective Disorders 99:9–17, 2007.
37. Yang M, Barner JC, Lawson KA, Rascati KL, Wilson JP, Crismon ML, Worchel J, Mascarenas CA: Antipsychotic medication utilization trends among Texas veterans: 1997-2002. Annals of Pharmacotherapy 42:1229–1238, 2008.
38. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, O'Donovan C, Macqueen G, McIntyre RS, Sharma V, Ravindran A, Young LT, Milev R, Bond DJ, Frey BN, Goldstein BI, Lafer B, Birmaher B, Ha K, Nolen, WA, Berk M: Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disorder 15:1–44, 2013.

Mehmet Kemal Arıkan is a professor at the Department of Psychiatry, Cerrahpaşa Faculty of Medicine, Istanbul University. He has experience in pharmacology, with emphasis on polypharmacy. His research has focused on the use of EEG, ERP, and neurocognitive measures of brain function and on the stigma of mental illness.

Cana Aksoy Poyraz is specialist at the Department of Psychiatry, Cerrahpaşa Faculty of Medicine, Istanbul University. In psychiatry, she has experience in psycphopharmacology, mood disorders and psychotic disorders.

Alper Baş is a resident at the Department of Psychiatry, Cerrahpaşa Faculty of Medicine, Istanbul University. He has experience in psychopharmacology, and mood disorders.

N. Gamze Usta Sağlam is a resident at the Department of Psychiatry, Cerrahpaşa Faculty of Medicine, Istanbul University. She has experience in clinical research and psychopharmacology.

Gizem Cetiner Batun is a resident at the Department of Psychiatry, Cerrahpaşa Faculty of Medicine, Istanbul University. She has experience in psychopathology and psychopharmacology.

Gözde Gültekin is a resident at the Department of Psychiatry, Cerrahpaşa Faculty of Medicine, Istanbul University. She has experience in biological psychiatry and psychopharmacology.

Burç Çağrı Poyraz is specialist at the Department of Psychiatry, Cerrahpaşa Faculty of Medicine, Istanbul University. In psychiatry, he has experience in geriatric psychiatry and psycphopharmacology. His research in has focused on the use of EEG, ERP, and neurocognitive measures of brain function.