The Increasing Use of Polypharmacotherapy for Refractory Mood Disorders: 22 Years of Study

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Background: Few studies have approached the subject of polypharmacotherapy systematically. This retrospective review of 178 patients with refractory bipolar disorder or unipolar depression (Research Diagnostic Criteria or DSM-III-R criteria) discharged from the National Institute of Mental Health (NIMH) Biological Psychiatry Branch between 1974 and 1996 was conducted to assess the degree and efficacy of "add-on" pharmacotherapy.

Method: Following completion of formal structured blinded research protocols, patients entered a treatment phase (often again on a blind basis) in which all agents available in the community could be utilized. Each patient's retrospective life chart and all prospective double-blind nurse- and self-rated NIMH data were reviewed. The overall degree of improvement at discharge was assessed by rating on the Clinical Global Impressions scale (CGI) as modified for bipolar illness (CGI-BP).

Results: A 78% improvement rate (moderate or marked on the CGI) was achieved at the time of discharge. There was a significant relationship between number of medications utilized at discharge as a function of discharge date ($r = 0.45$, $p < .0001$). The percentages of patients discharged on treatment with 3 or more medications were 3.3% (1974–1979), 9.3% (1980–1984), 34.9% (1985–1989), and 43.8% (1990–1995). No correlation was found between polypharmacy and age ($r = –0.03$, $p = .66$). Patients more recently discharged from the NIMH had an earlier age at illness onset, more lifetime weeks depressed, and a higher rate of rapid cycling than patients in the earlier cohorts.

Conclusion: Increasing numbers of medications in more recent NIMH cohorts were required to achieve the same degree of improvement at hospital discharge. More systematic approaches to the complex regimens required for treatment of patients with refractory mood disorder are clearly needed.

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"The true polypharmacy is the skillful combination of remedies." —Sir William Osler[1]

Patients with refractory mood disorder, particularly manic-depressive illness, are commonly treated with multiple medications. Circa 1996, these medications primarily included lithium and the anticonvulsants carbamazepine and divalproex sodium, as supplemented by calcium channel blockers, conventional antidepressants, benzodiazepines, antipsychotics, and thyroid hormone.

Lithium carbonate has clearly been the gold standard for treatment of acute mania and bipolar depression and for long-term maintenance treatment.[2] However, the failure rate for lithium in acute mania has been reported in recent reviews to be 50% or higher.[3,4] For example, in the largest double-blind, randomized study of lithium and valproate to date,[5] the response rate (defined as a 50% reduction in manic severity) to either of these agents at the end of the 3-week study period was only 50%. Furthermore, patients who have some bipolar subtypes have particularly poor responses to lithium, including those with mixed or dysphoric mania,[6] rapid cycling,[7] a depression-mania-well interval sequence,[8] and substance abuse comorbidity.[9–11]

Although the mood-stabilizing anticonvulsants provide treatment alternatives, some patients fail to respond acutely or prophylactically to carbamazepine and divalproex sodium, and others can gradually develop loss of efficacy or tolerance.[3] Although early observations of the acute efficacy of a new generation of potential mood-stabilizing anticonvulsants (gabapentin and lamotrigine) look promising,[12–15] further controlled studies are encouraged.

Often, polypharmacotherapy is needed for maximal stabilization. This is not infrequent clinical practice in the

medical management of tuberculosis,[16] congestive heart failure,[17] autoimmune disorders,[18] multiple sclerosis,[19] acquired immunodeficiency syndrome,[20] immunosuppression in transplantation,[21] and refractory epilepsy.[22] In fact, lamotrigine and gabapentin received their recent U.S. Food and Drug Administration (FDA) approval utilizing "add-on" designs.[23,24] Furthermore, lamotrigine and valproate have what appears to be pharmacodynamic synergy with anticonvulsant effects[25] and enhanced efficacy for mood stabilization.[26,27] However, few clinical studies in affective disorder have incorporated this design, and no FDA approvals have been based on such adjunctive clinical trials.

The most common mode of polypharmacotherapy (or complex combination therapy) utilized in psychiatry is "add-on" or adjunctive pharmacotherapy. The prevalence of this practice has been reported to exist in 28% to 75% of diverse patient populations and study designs and is reviewed extensively by Rapp and Kaplan[28] and Gardos et al.[29] More recent reviews, both in bipolar illness[30,31] and unipolar depression,[32,33] continue to suggest that this is a very common practice.

In the National Ambulatory Medical Care survey, psychiatric practice, compared with other medical specialties, was predictive of greater use of polypharmacotherapy, and manic patients were 4 times more likely to receive multiple medications than nonpsychiatric patients.[34] When lithium is prescribed, greater than 70% of the time it is utilized in combination strategies.[34–37] This polypharmacotherapy has been reported to be more prevalent in women and to increase with age.[35] Furthermore, some point prevalence studies have noted an increasing rate of polypharmacotherapy in more recent study cohorts.[38,39] The study by Hallin et al.[39] noted single-agent therapy (48% lithium) in 57% of 240 bipolar patients in 1989; in contrast, single-agent therapy (26% lithium) was used in only 37% of 190 patients 5 years later in 1994. Neither of these studies assessed baseline severity of illness or the degree of improvement on combination treatment.

Peselow et al.,[40] in a large naturalistic study of lithium prophylaxis for patients with bipolar illness (N = 305), reported that the probability of remaining euthymic was 85%, 52%, and 37% after 1, 3, and 5 years of lithium monotherapy, respectively. For an affective relapse, patients were treated with lithium plus an adjunctive mood stabilizer, antidepressant, neuroleptic, or benzodiazepine; 70% of these patients did better on combination treatment and obtained greater protection against subsequent relapse when compared with the initial course of lithium monotherapy.

Few studies have approached the subject of polypharmacotherapy systematically, and it is the purpose of this article to initiate such a discussion. This retrospective review of 178 patients with refractory mood disorder discharged from the 3-West Clinical Center Research Unit of the Biological Psychiatry Branch (BPB), National Institute of Mental Health (NIMH), between 1974 and 1995 was conducted to assess the degree and efficacy of "add-on" polypharmacotherapy utilized on a double-blind basis.

METHOD

The referral base for the BPB, NIMH, is refractory unipolar and bipolar patients (meeting Research Diagnostic Criteria or, more recently, DSM-III-R criteria) who have failed usual therapies in the community and who wish to participate in intensive neurobiological evaluation and clinical treatment utilizing double-blind protocols.

Patients sequentially discharged from the Unit from 1974 to 1996 were included in the analysis if they completed one or more double-blind monotherapy protocols and associated research procedures and wished to remain on the Unit to begin a more clinically based treatment phase of hospitalization. This was, again, often conducted on a blind basis utilizing alternative and add-on medication in an attempt to further treat and acutely stabilize their refractory affective illness. There was no standard clinical algorithm for the study group; each patient's case was evaluated separately taking into account initial double-blind, protocol-driven monotherapy, drug trial responsiveness, past drug trials prior to NIMH, and clinical tolerability. The vast majority of patients had experienced multiple unsuccessful clinical trials prior to their NIMH admission.

Patients gave informed consent for a placebo period of evaluation and for each of the protocol medications under clinical research investigation. This first included a major monotherapy research focus on piribedil[41] and pimozide,[42] and then, sequentially, carbamazepine,[43,44] valproate,[45] thyrotropin-releasing hormone (TRH), nimodipine,[46] lamotrigine,[47] and gabapentin.[47] Patients almost always continued taking double-blind medications throughout the hospitalization; i.e., neither they nor the nursing staff were aware of when they were on active medication or the sequence of new monotherapies and then "add-on" medication trials including conventional antidepressants, benzodiazepines, neuroleptics, and thyroid hormones. Only in the last year of the study (1995) were patients aware of when they were in a given 6-week phase (1, 2, or 3) comparing lamotrigine, gabapentin, and placebo on a randomized crossover basis.[15]

Double-blind ratings consisted of twice-daily nurses' ratings by consensus using the 15-point Bunney-Hamburg Rating Scale for depression, mania, anger, anxiety, and psychosis[47] and a self-rating of mood utilizing a 100-mm visual analog scale. These daily longitudinal measures were depicted graphically for comparison with prior course of illness, as assessed by the retrospective life chart method (NIMH-LCM).[48] The NIMH-LCM allows for systematic quantification of a number of course-of-illness variables including age at time of first symptoms, duration of illness, and past hospitalizations. Not all of the 178 patients had a

retrospective life chart as reflected in age at onset (N = 160) and lifetime weeks of depression (N = 138) correlations to discharge date.

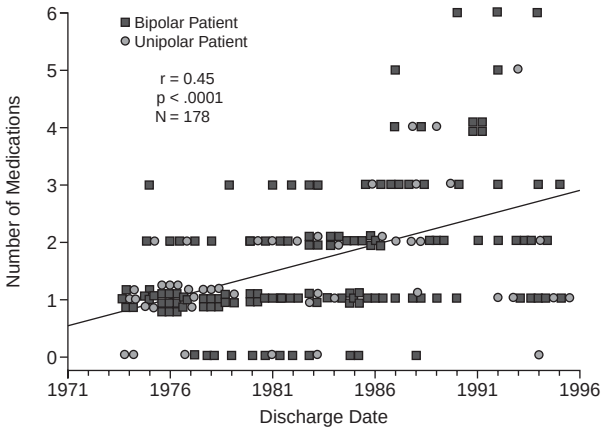
The demographic profile of the 178 patients included 131 with bipolar disorder (76, bipolar I; 50, bipolar II; 5, schizoaffective bipolar type) and 47 with recurrent unipolar depression (5 schizoaffective depressed type); 108 female and 70 male patients were included. The mean ± SD patient age at discharge was 40 ± 12.8 years; women were older (42.1 ± 12.3 years) than men (36.9 ± 12.9 years, $p < .008$). There was no correlation between age and discharge date (N = 178, r = 0.04, $p < .64$), suggesting that age at discharge remained relatively constant over the 22-year period. The mean ± SD duration of prior illness was 17.3 ± 11.2 years (N = 160).

The NIMH-LCM retrospective clinical demographics examined by gender revealed a longer duration of illness for women (mean ± SD = 19.8 ± 10.9 years, N = 99) than for men (13.3 ± 10.5 years, N = 61; $p < .0002$), a greater number of hospitalizations for depression for women (mean ± SD = 4.5 ± 5.83, N = 91) than for men (2.5 ± 3.53, N = 55; $p < .02$), and a greater number of lifetime weeks of depression for women than for men (Mann-Whitney U mean rank = 57.8 for women versus 41.3 for men, N = 103; U = 820.5, $p < .01$). When age, duration of illness, and lifetime weeks depressed were controlled for, gender difference remained significant ($p < .007$, $p < .05$, respectively). No significant differences in age at discharge ($p = .89$) or duration of illness ($p = .7$) by bipolar versus unipolar subtype were found.

The overall rating of improvement at discharge was made by the Clinical Global Impressions scale (CGI) as modified for bipolar illness (CGI-BP),[49] which allows for rating of degree of clinical improvement in depression, mania, and overall illness. Moreover, it addresses many of the specific criticisms leveled at the CGI relating to the types of ratings, technical and scaling problems, definition of time domain of the rating, and confounding of clinical response with tolerability and side effects. The main measure was degree of overall clinical improvement at discharge, as assessed from the patients' most appropriate worst phase of illness, which almost invariably was during their period of baseline evaluation while receiving placebo. Degree of improvement was classified as marked (essentially complete remission), moderate (distinct clinically important improvement, but some symptoms remain), mild (slight but insufficient to affect patient's basic clinical status or functioning), or no change or similar degrees of worsening, as described in detail elsewhere.[49]

Degree of clinical global response achieved at discharge was subsequently analyzed as it related to the major demographic and course-of-illness variables available from the NIMH-LCM. Statistical analysis was conducted using SPSS software (version 8.0; Chicago, Ill.). Pearson r correlations between discharge date and other NIMH-LCM variables were calculated. A stepwise multiple regression analysis was performed on these variables using number of medications at discharge as the dependent variable. Unipolar and bipolar subgroups were analyzed separately, but when no major differences were observed, they were combined for the sake of brevity of presentation. Means are reported including ± standard deviation. Group differences were compared using the Student t test except where extreme outliers required the use of the Mann-Whitney U test.

Figure 1. Increasing Polypharmacotherapy in More Recent National Institute of Mental Health (NIMH) Discharges



RESULTS

The overall response rate as measured by CGI score at the time of hospital discharge was 78% (35% marked improvement, 43% moderate improvement). Of the 21% who were nonresponders, 16% were mildly improved, 4% showed no change, and 1% were mildly to moderately worse. The analysis of CGI versus date of discharge yielded a weak positive correlation (r = 0.20, $p < .007$), showing that the patients more recently discharged from the NIMH were, if anything, slightly more improved than those studied earlier.

There was a highly significant positive relationship between increased number of discharge medications and the more recent discharge date (r = 0.45, $p < .0001$; N = 178; Figure 1). There was no correlation between the degree of polypharmacotherapy and age at discharge (r = –0.03, $p = .66$). Length of hospital stay correlated with discharge year (r = 0.432, $p < .0001$) and the number of discharge medications (r = 0.34, $p < .0001$); i.e., more recent patients had longer hospitalizations, most likely related to the greater number of blinded monotherapy and add-on trials available and offered to patients who remained unimproved in their clinical treatment phase of their hospi-

Table 1. Adjunctive Medication to Primary Mood Stabilizer at NIMH Discharge

Adjunctive Medication, N (%)	Lithium (N = 55)		Carbamazepine (N = 49)		Divalproex Sodium (N = 12)		Calcium Channel Blocker (N = 7)[a]		Total (N = 123)	
	Unipolar (N = 9)	Bipolar (N = 46)	Unipolar (N = 11)	Bipolar (N = 38)	Unipolar (N = 0)	Bipolar (N = 12)	Unipolar (N = 1)	Bipolar (N = 6)	Unipolar (N = 21)	Bipolar (N = 102)
Any adjunctive medication	5 (56)	12 (26)	6 (55)	23 (61)	0	12 (100)	1 (100)	2 (33)	12 (57)	49 (48)
Antidepressant	3 (33)	6 (13)	2 (18)	6 (16)	0	4 (33)	0	2 (33)	5 (24)	18 (18)
Neuroleptic	1 (11)	4 (9)	0	5 (13)	0	1 (8)	0	0	1 (5)	10 (10)
Benzodiazepine	0	1 (2)	0	2 (5)	0	0	0	0	0	3 (3)
Calcium channel blocker	0	1 (2)	1 (9)	0	0	1 (8)	0	0	1 (5)	2 (2)
Thyroid	3 (33)	2 (4)	1 (9)	4 (11)	0	7 (58)	0	0	4 (19)	13 (13)

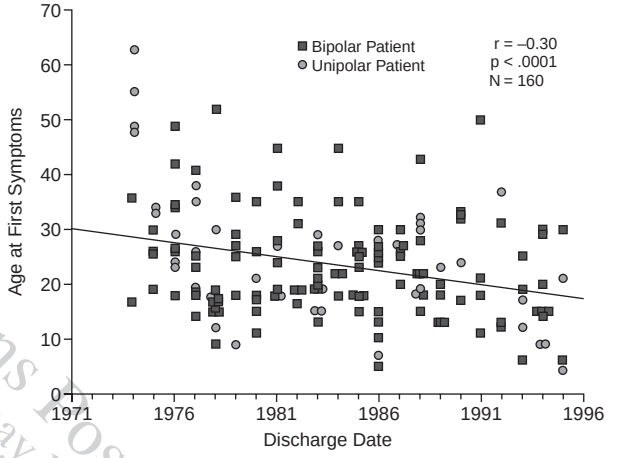
[a]A total of 10 patients were discharged on treatment with a calcium channel blocker, only 3 of them as an adjunctive medication.

talization following the protocol-driven research phase. However, the partial correlation between discharge date and number of medications, controlling for length of hospital stay, was still significant ($r = 0.36$, $df = 175$, $p < .001$). The significance remained when controlling for rapid-cycling status ($r = 0.32$, $df = 159$, $p < .001$). Moreover, for statistical confirmation, a stepwise multiple regression analysis was performed evaluating the continuous variables such as age at discharge, age at illness onset, past hospitalizations for depression, length of NIMH hospitalization, and discharge date with number of discharge medications as the dependent variable. The only variable showing significance was discharge date ($R^2 = 0.182$, $t = 4.60$, $p < .0001$).

By arbitrarily defined epochs, the mean number of discharge medications for 1974–1979 was 1.5; for 1980–1984, 1.5; for 1985–1989, 2.5; and for 1990–1995, 3.0. The percentages of patients discharged on treatment with 3 or more medications in these same epochs were 3.3%, 9.3%, 34.9%, and 43.8%, respectively. The degree of clinical global improvement on the CGI-BP was not correlated with the number of discharge medications ($r = 0.09$, $p < .26$; $N = 178$).

Table 1 summarizes the types of adjunctive discharge medication to 4 major mood stabilization treatment groups sequentially utilized (lithium, carbamazepine, divalproex, and calcium channel blockers). Over the entire study period, for those patients who were discharged on treatment with a mood stabilizer ($N = 123$), adjunctive medications included conventional (or unimodal) antidepressants (18.7%), thyroid supplementation (13.8%), neuroleptics (8.9%), benzodiazepines (2.4%), and calcium channel blockers (2.4%). In comparison with bipolar patients discharged on treatment with fewer than 2 medications, bipolar patients who were discharged on treatment with 2 or more medications were more likely to be rapid cyclers (Fisher exact test, $p = .04$). There was no difference in monotherapy versus polytherapy (i.e., ≥ 2 medications) by gender, age at discharge, or age at illness onset. Remarkably, the unimodal antidepressants and neuroleptics, while used as necessary when other agents were not effective, did not constitute a major portion of the discharge medications for this group of refractory patients.

Figure 2. Earlier Onset of Symptoms in More Recent NIMH Cohorts



A number of NIMH-LCM retrospective demographic variables that might be related to the increasing use of polypharmacy were examined. When the age at onset of first mood symptoms was assessed, a significant decrease over time ($r = –0.30$, $p < .0001$; $N = 160$) was noted; i.e., the patients more recently discharged from the NIMH reported earlier symptom onset than patients who were discharged earlier (Figure 2). Secondly, over the 22-year period, there was a concomitant pattern of increasing duration of lifetime weeks of depression experienced prior to NIMH hospitalization as a function of discharge date ($r = 0.28$, $p < .001$; $N = 138$).

There was also an increase in the percentage of rapid cyclers over the study period. In the 1970s, rapid cyclers constituted 30% of the population; in the 1980s, 56%; and in the 1990s, 70% ($\chi^2 = 14.66$, $p < .001$). The rapid cyclers, in comparison with non–rapid cyclers, had a longer

duration of illness ($t = 2.86$, $df = 116$, $p = .005$), more past hospitalizations for depression ($t = 2.05$, $df = 92$, $p = .04$), and a trend for a greater number of medications at discharge ($t = 1.74$, $df = 119$, $p = .08$).

DISCUSSION

Several assets and liabilities are apparent in the interpretation of this study. One of many liabilities of this study was that it was conducted in a research setting and improvement was based only on status at discharge; confirmation of more substantial and sustained clinical efficacy requires longer-term follow-up, which is in progress. Secondly, there was no precise clinical algorithm under which all patients were treated. This option was precluded because of the evolution in research focus and potential therapeutic agents evaluated over the study period. However, after primary research evaluations and monotherapy protocols were completed, the general pattern was to target current symptomatology in sequential, blinded monotherapy and then use add-on clinical trials in an attempt to maximize mood stability on an individualized basis. This would be attempted using all prior information (i.e., retrospective life chart) and the patient's carefully observed course of illness at the NIMH. Although viewed as a limitation for development of a large-scale algorithm, the general use of sequential add-on clinical trials does, to some extent, parallel clinical practice, although in a blinded fashion. Finally, the potential implications that this unique treatment-refractory, increasingly rapid-cycling cohort has for the general population of patients in a practice setting must be cautiously and conservatively considered.

One of the study assets was that virtually all of the medication trials were conducted on a double-blind basis. Secondly, clinical response to an initially blind protocol medication was often reconfirmed with a phase of placebo substitution and rechallenge with the active agent. Thirdly, extensive life chart data were available on each patient, so that the likelihood of a placebo response or a response attributable to the natural course of illness could be factored into the clinical and research evaluations in further attempting to determine clinical improvement at discharge not likely related to spontaneous illness variation. Finally, the primary research goal of the initial phases of study allowed for a more extended continuation of the blind evaluations that would not be possible in most clinical settings.

Despite the liabilities noted above, several preliminary conclusions about the increasing need for combination treatment at discharge nevertheless can be drawn. The relatively low percentage in bipolar and unipolar patients of the use of adjunctive antidepressants (bipolar, 18%; unipolar, 24%) and neuroleptics (bipolar, 10%; unipolar, 5%) in discharge regimens, despite a highly favorable overall improvement rate of 78%, was surprising. This is at variance with most traditional clinical treatment units in which patients with acute mania or rapid cycling, under pressure of short-term hospitalizations, are almost uniformly exposed to and treated with neuroleptics. A recent review noted 40% to 72% of bipolar patients were currently treated with an antipsychotic and 90% to 100% had history of neuroleptic exposure.[50] Secondly, as reviewed by Frye et al.,[51] typical neuroleptics have significant liability for lack of mood stabilization, acute extrapyramidal symptoms, and tardive dyskinesia in bipolar patients. In the course of exposing fulminantly manic patients to alternative investigatory and now more routinely used agents such as carbamazepine and valproate, we uncovered this general lack of necessity for neuroleptic use even in this highly treatment-refractory rapid-cycling population.

At the opposite pole, the potential liability of unimodal antidepressants to precipitate acute manic episodes or induce cycle acceleration in bipolar patients has been noted by many investigators.[52–54] Again, the vast majority of this unusually treatment-refractory population, overrepresented with rapid cyclers compared with most community settings, were able to be discharged without the use of conventional antidepressants. When conventional antidepressants were used, this was almost always in the context of one or more mood stabilizers.

The sequential pharmacotherapy and add-on approaches were utilized under the general rubric of using new agents with potentially different mechanisms of action, as well as specific targeting of remaining symptoms and illness patterns in an attempt to achieve a more robust or complete therapeutic effect, as discussed elsewhere.[55] It is our impression that these at times complex psychopharmacologic regimens were well tolerated because of the use of the principle of titrating to reach greatest efficacy with fewest side effects (rather than targeting specific dose or blood level windows). These data thus do not directly address important issues regarding the potential for added toxicity, teratogenicity, or noncompliance with combination treatments.[56–58]

Several possibilities could account for the observed need for increased multimodal medication regimens used at hospital discharge. This could be driven by (1) more clinical treatments available; (2) more extensive treatment of patients in the community prior to referral to the clinical research programs of the NIMH, such that cohorts of the more treatment-refractory patients were referred; (3) increased severity of illness due to a changing referral bias for earlier-onset rapid cyclers; and/or (4) an increasing severity or refractoriness of illness in the general population, such that the need for polypharmacotherapy was reflective of a similar trend in the community at large. The latter possibility cannot be dismissed altogether in light of the evidence for a cohort effect for unipolar and bipolar illness[59,60] attributable to a variety of potential causes, including genetic anticipation.[61]

What trends in the characteristics of this patient population are consistent with one or more of these possibilities? Over the study period, patients were admitted with a progressively earlier age at illness onset and an increased incidence of rapid cycling. Taken together, these data suggest that a generally more ill and treatment-refractory group based on course-of-illness characteristics were admitted to the NIMH over the study period. Perhaps data on number of unsuccessful medication trials prior to NIMH referral over the study period would be most telling about past treatment refractoriness. These data are not currently available in a systematic fashion, but it is our impression that bipolar patients referred to the NIMH were generally lithium refractory in the decade of the 1970s, lithium and carbamazepine refractory in the decade of the 1980s, and, in the 1990s, lithium, carbamazepine, and valproate refractory. This might suggest that patients in recent cohorts were more extensively treated in the community prior to their referral to a tertiary clinical research unit such as the NIMH. Whatever the basis for the referral of the more ill patients, as inferred from their prior course-of-illness variables, there was a highly significant relationship of increased numbers of medications utilized in the more recently discharged patients ($r = 0.45$, $p < .0001$; $N = 178$). This occurred while maintaining or slightly enhancing the overall degree of improvement achieved at discharge over the study period.

It is particularly disheartening to note that, aside from lithium, there are no FDA-approved agents for long-term prophylaxis of bipolar illness. Furthermore, there have been no recent attempts at approval of "add-on" drug regimens for the large group of refractory bipolar patients, whereas this has been the mode of approval for the last 4 anticonvulsants for refractory epilepsy patients. Moreover, few acute or long-term clinical trials in bipolar illness have been funded by the NIMH in the past decade[62]; thus, bipolar patients not responsive to lithium and other commonly used therapies are treated prophylactically, without the benefit and guidance of a systematic clinical trials literature.

There are also no controlled studies of the relative merits of aggressive early-intervention polypharmacotherapy as opposed to the late salvage polypharmacotherapy described here. This is in marked contrast to polypharmacotherapy in reducing human immunodeficiency viral load[63] or the clinical practice of combination chemotherapy for malignancy. Polypharmacotherapy may be an underutilized strategy for achieving maximal mood stability given the potential clinical and neurobiological consequences of an inadequately treated illness; i.e., increased severity, cycling, and refractoriness.[3]

Although this retrospective study has many limitations (i.e., retrospective review, lack of precise algorithm or prospective follow-up data, and a treatment-refractory population screened for willingness to participate in neurobiological and clinical trials research), it does impart the great need for further studies in recurrent affective illness to clarify the relationship of comorbidities and course-of-illness characteristics to the subsequent degree of polypharmacotherapy and long-term efficacy. In managing refractory mood disorders with complex polypharmacotherapies, tolerability of agents needs to be vigorously monitored to ensure safety and tolerability, especially since complex regimens have been associated with noncompliance.[58]

Given the increasing number of agents available in the bipolar and unipolar pharmacopoeia, controlled study of combination therapy (both "add-on" and aggressive "at-onset" polypharmacotherapy) could only benefit the development of optimal and empirically based algorithms for achieving maximal mood stabilization in the large population of patients with difficult-to-treat affective illness.

Drug names: carbamazepine (Tegretol and others), divalproex sodium (Depakote), gabapentin (Neurontin), lamotrigine (Lamictal), nimodipine (Nimotop), pimozide (Orap).

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