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REVIEW

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Lithium: Still a Major Option in the Management of Bipolar Disorder

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SUMMARY

Still after more than 50 years, lithium is a major treatment of bipolar disorder, even though it has not been promoted by the pharmaceutical industry over the last decades. In recent years the evidence base on lithium for bipolar disorder has substantially increased due to results from a number of trials. Therefore, a review of this evidence is timely. The efficacy of lithium as an acute treatment and as a maintenance treatment of bipolar disorder was evaluated through a review of the evidence, focusing on modern, randomized, parallel-group designed trials. Additionally, the evidence was sought translated into the proper use of lithium in clinical practice. Lithium's antimanic efficacy has been convincingly demonstrated. However, as blood monitoring due to the risk of toxicity is required and due to an insufficient response in highly agitated patients, lithium monotherapy has a limited place in the acute treatment of severe manic states. For acute bipolar depression, results are conflicting. Recent maintenance trials have added substantially to the documentation of lithium's long-term stabilizing properties in bipolar disorder, and these properties have been demonstrated independently of any acute response to lithium. Finally, it is now beyond doubt that not only does lithium prevent mania, but also depression in bipolar disorder. Lithium is still to be considered a major if not the most important mood- stabilizer, at least for maintaining long-term stability in patients with bipolar disorder. The potential risks of lithium should be weighed up against its benefits and the fact that serious adverse effects are usually avoidable.

Introduction

When in 1949 Cade [1] serendipitously discovered lithium as a potential drug for acute mania, it was a fundamental milestone in the development of psychiatric treatment. Until the early 1990s lithium was in fact the only robust alternative to the use of typical antipsychotics for the treatment of acute mania [2]. Early studies also suggested an acute efficacy of lithium in bipolar depression [3], and in the 1970s lithium was established as the standard treatment in maintenance [4].

It has been debated whether there has been a declining interest in lithium over the last decade. A recent National Institute for Health and Clinical Excellence report (Bipolar disorder, clinical guideline 38, December 2009) demonstrated that the prescription rate of lithium at least in England was fairly stable from 2000 to 2009. However, given an increased focus on the identification and treatment of bipolar disorder over the same time period, the seemingly stable use of lithium in absolute terms might indicate an increased use of alternative mood-stabilizing agents. On the other hand, given the pharmaceutical industry's massive promotion of these alternatives during the period, the figures may also give rise to the interpretation that lithium is indeed still an established drug.

In recent years the evidence base on lithium for bipolar disorder has substantially increased due to results from a number of Randomized Clinical trials (RCTs), both investigator-sponsored trials and industry-sponsored approval trials, the latter often including lithium as an internal standard. Therefore, a review of this evidence is timely.

Aims and Methods

The efficacy of lithium as an acute treatment and as a maintenance treatment of bipolar disorder was evaluated through a review of the evidence and its development over time, focusing on large, conclusive, randomized, and parallel-group designed trials. In a final section of the paper, a translation of the evidence into clinical practice was attempted, including a brief discussion of the adverse effects and recommendations on the proper use of lithium.

Beyond its mood-stabilizing actions, lithium has potential beneficial actions in other domains of relevance to the management of bipolar disorder. Thus, lithium is believed to possess antiaggressive and antisuicidal actions [5–7]. Additionally, an effect in neurodegenerative disorders has been suggested [8,9]. However, these

potential actions will not be covered here. Also, the basic pharmacodynamics of lithium will not be covered (see e.g., [10,11]).

Acute Antimanic Actions of Lithium

Evidence of Efficacy *per se*

After Cade's [1] observation had been confirmed by four placebo-controlled cross-over studies conducted between 1954 and 1971 as reviewed by Goodwin and Jamison [4], the antimanic efficacy of lithium was evaluated in several comparative RCTs conducted from 1970 to 1980, using chlorpromazine or haloperidol as the reference drug. Most of these studies found lithium to be as least as effective as the comparator; however, sample sizes were generally small [2,12]. In the largest and only conclusive of these studies, chlorpromazine was superior to lithium in the highly active patients whereas in the mildly active, lithium and chlorpromazine were comparable [13]. From 1980 and onwards, other putative antimanic agents were compared to lithium in a number of small, investigator-sponsored, essentially inconclusive trials, albeit all supporting antimanic potentials of lithium [2,12].

In 1994, Bowden et al. [14] provided the final proof that lithium is an antimanic drug. In this study, which was the first placebo-controlled parallel group designed study on lithium in mania, response rates of 49%, 48%, and 25% for lithium, valproate and placebo, respectively, were found over a period of three weeks. For lithium the Number Needed to Treat (NNT) was 5 (95% CI: 3–22). Response was defined as a 50% reduction or more on the applied mania rating scale setting the standard for future trials. This methodologically innovating RCT was followed by other similar approval trials, using lithium as an internal standard to validate assay sensitivity. Thus, lithium was also superior to placebo in a study with quetiapine as the investigational drug [15], in two studies with topiramate as investigational drug [16], and in one study with aripiprazole as investigational drug [17]. In two unpublished studies with lamotrigine as investigational drug (GlaxoSmithKline study SCA 2008 and SCA 2009) lithium did separate numerically, but not statistically significantly from placebo. However, in SCA 2009 lithium almost reached the level of statistical significance. In a meta-analysis including these pivotal studies except the one by Keck et al. [17], a NNT (lithium versus placebo) of 6 (95% CI: 4–13) was found [18]. In terms of NNT, the benefit of lithium relative to placebo is similar to that of other antimanic drugs.

Two recent well-powered comparative RCTs found lithium to be inferior to olanzapine over 4 weeks [19] and lithium to be comparable to valpriate over 12 weeks [20], respectively.

Lithium Combined with Other Antimanic Drugs

Several drug companies have found that their atypical antipsychotic added to lithium or valproate was superior to placebo added to lithium or valproate in manic patients partially nonresponding to lithium or valproate [21–25]. However, since the ratio between the number of patients insufficiently responding to prophylactic lithium/valproate and the number of patients insufficiently responding to acute lithium/valproate was not described in these reports, interpretation is difficult. These findings do not add directly to the evidence of efficacy of lithium, but indirectly they may indicate that lithium and the antipsychotics may work through different mechanisms in mania.

It should be born in mind that the modern RCTs reviewed above all allowed concomitantly use of benzodiazepines which in themselves may have augmenting potentials [26,27] compensating (at least in part) for a potentially delayed onset of action of lithium.

Efficacy in Subgroups

Besides severe agitation being a negative predictor of response to lithium (in comparison to chlorpromazine) [13], depressive symptoms during mania have been shown to predict a poorer response to lithium (in comparison to valproate) [28]. When psychotic symptoms are present in the context of mania, there is some evidence indicating that lithium works equally well as antipsychotics [15,29,30] and valproate [31]. However, a few earlier, small studies indicated some additive effect of lithium and a typical antipsychotic in combination in manic patients with psychotic symptoms [32–34].

Time Course of Response

In three of the early RCTs comparing a typical antipsychotic with lithium, the antipsychotic seemed to have a more rapid onset of action than lithium [13,35,36]. In contrast, in the two pivotal studies evaluating valproate [14] and quetiapine [15], respectively, no differences were observed in the time courses of response between the investigational drug and lithium. Similar time courses were also seen in the lithium and in the valproate groups in the 12 week comparative study mentioned above, in which the oral loading strategy for valproate was applied [20]. In comparison with aripiprazole, lithium's onset of action appeared to be delayed [17].

Evidence on Dosing in Mania

When manic patients were randomized into three different dosing levels and placebo, using a complex alternating treatment schedule, a statistically significant relation between serum–lithium (up to 1.4 mEq/L) and antimanic response was demonstrated [37]. It is likely that a rapid uptitration of lithium [38], in contrast to the more cautious one usually applied, will forward the onset of action of lithium. However, due to lithium's low therapeutic index such strategies carry a risk of toxicity [4].

Acute Antdepressive Actions of Lithium

Evidence of Efficacy in Acute Bipolar Depression

Eight of nine small placebo-controlled RCTs have indicated that lithium has beneficial actions in acute bipolar depression [3]. However, these trials have various methodological shortcomings [39]. In a recent industry-generated RCT which aimed at testing the efficacy of quetiapine against placebo in bipolar depression, lithium was incorporated to ensure the validity of the design [40]. At

study end (at week 8) there was a numerical advantage of lithium over placebo but statistically only a trend of separation. However, serum concentrations of lithium were relatively low (mean 0.61 mEq/L).

Evidence on Dosing in Depression

Adding paroxetine or imipramine to low-dose lithium (serum–lithium at 0.8 mEq/L or below) in acutely bipolar depressed patients was shown to be superior to adding placebo, whereas in patients on high-dose lithium (serum–lithium above 0.8 mEq/L) no such superiority was seen [41]. The differential effect could be attributed to a high response rate in the high-dose (plus placebo) group, and although patients were not allocated to the lithium groups randomly, a serum-lithium response relation was inferred. A relation between lithium dose and the augmenting effect of lithium in unipolar depression has also been indicated, with doses above 600–800 mg lithium carbonate being effective [42].

Lithium's Long-Term Mood-Stabilizing Properties

Evidence of Relapse/Recurrence Prevention from Placebo-Controlled RCTs

Following Baastrup and Schou's [43] observation in 1967 of lithium decreasing the frequency of episodes in bipolar disorder (and in recurrent unipolar depression), a number of early placebo-controlled RCTs (1970–1978) established the long-term efficacy of lithium in bipolar disorder as reviewed by Goodwin and Jamison [4]. Twenty years later, a series of industry-sponsored long-term studies, aiming at regulatory approval of alternatives to lithium and using lithium as an internal standard, began to appear. In 2004, Geddes et al. [44] included the first three of these studies [45–47] together with two earlier studies [48,49] in a meta-analysis for the evaluation of lithium. These studies were characterized by pure samples of bipolar patients and by study patients being maintained and stabilized on lithium for no more than 3 months prior to randomization, and lithium was confirmed to be statistically significantly superior to placebo [44]. However, the effect size (2-years' relapse/recurrence rates of 40% and 60% on lithium and placebo, respectively) was less than reported in earlier analyses [4,50], partly due to the inclusion of the essentially failed RCT by Bowden et al. [45] which aimed at testing valproate against placebo. The two studies included, which were designed with the purpose of obtaining regulatory approval of lamotrigine were remarkable in that the lithium arm was incorporated in a nonenriched way, meaning that lithium (in contrast to lamotrigine) was tested independently of showing any mood-stabilizing effect and tolerability during the index episode prior to randomization [46,47]. Recently, lithium was used as the internal standard in an approval study testing the preventive actions of quetiapine against placebo in bipolar patients with an index episode of mania, depression or mixed state responding acutely to the investigational drug [51]. Again, lithium (as monotherapy) was introduced at randomization after remission had been obtained, that is, independently of showing any acute effect and tolerability, and again it was clearly superior to placebo.

Since enriched conditions as exemplified here above may increase the likelihood of finding a signal over placebo in comparison with the likelihood of finding a signal under nonenriched conditions, it is worth noticing that lithium in fact is the only drug that has been proved to possess preventive effects in bipolar disorder under non-enriched conditions.

Prevention of Mania Versus Depression

Up till 1990, there was no substantial evidence contradicting that lithium prevents mania and depression equally well [4]. In the meta-analysis by Geddes et al. [44], only numerical (but not statistically significant) superiority of lithium over placebo in the prevention of depression could be detected. This finding was seemingly driven by the pivotal lamotrigine studies [46,47]. However, in the approval study of quetiapine mentioned above, lithium clinically and statistically significantly prevented depression and mania equally well [51]. In the BALANCE trial, which was an open investigator-sponsored RCT, lithium prevented depression statistically significantly better than valproate [52].

Lithium Compared to Other Potentially Prophylactive Agents

In the pivotal lamotrigine studies, one recruiting patients with an index episode of depression [47] and the other recruiting patients with an index episode of mania [46], lamotrigine and lithium were comparable in terms of time to any mood episode. In a combined analysis of the two studies, lithium did statistically significantly better than lamotrigine in the prevention of mania, whereas lamotrigine did numerically (but not statistically significantly) better than lithium in the prevention of depression [53]. When lithium and lamotrigine were directly compared in a nonenriched sample in an open investigator-sponsored RCT, again no differences in risk of any relapse/recurrence could be demonstrated [54]. When breaking down the relapses/recurrences by polarity the same tendency as mentioned above appeared.

In other investigator-sponsored RCTs not favoring any of the comparators, lithium was found to be superior to carbamazepine [55–57]. Most recently, the BALANCE study indicated a superiority of lithium over valproate [52].

In the approval study of quetiapine [51], lithium performed on par with quetiapine, even though quetiapine was favored due to enrichment as described earlier. Lithium has also been tested against olanzapine in a noninferiority design in which patients having responded acutely to a combination of olanzapine and lithium were randomized [58]. In terms of any relapse/recurrence lithium and olanzapine were comparable, but olanzapine did statistically significantly better in terms of manic relapses/recurrences.

Lithium in Combination with other Potentially Prophylactic Drugs

The BALANCE study referred to above primarily tested a combination of valproate and lithium against each drug given as monotherapy, and even the combination did numerically better than lithium, the difference was not statistically significant [52]. A few other long-term RCTs have evaluated the efficacy of lithium in combination with alternative prophylactic agents. Thus, quetiapine [59] and olanzapine [60], respectively, in combination with lithium (or valproate) were shown to be superior to lithium (or valproate) plus placebo, albeit for the latter comparison not on the primary outcome measure [60]. However, in these trials, the randomized samples were enriched with patients who responded acutely to the combination, thereby increasing the likelihood of superiority of the combination in the long-term comparison. Additionally, a substantial proportion of the included patients may have shown a previous insufficient prophylactic response to lithium. The benefit of combining quetiapine and lithium has also been indicated in an observational study [61]. However, due to the lack of randomization, caution in interpretation is needed.

As to the combination of an antidepressant and lithium versus lithium monotherapy, a recent metaanalysis based on five mostly elder RCTs could not demonstrate any benefit from the combination therapy [62].

Evidence on Dosing in Maintenance

When bipolar patients were randomized to higher serum–lithium levels (0.8–1.0 mEq/L) or lower levels (0.4–0.6 mEq/L) the higher levels were more effective in terms of prevention of manic/mixed episodes, but not depressive episodes [63]. The findings may have been influenced by a relatively abrupt lowering of lithium dose at the time of randomization giving rise to potential rebound mania in those who had previously responded to a higher individualized lithium level [64]. However, two recent *post hoc* analyses on data set from two different RCTs confirmed that serum–lithium levels above 0.6 mEq/L seemed beneficial for the prevention of mania whereas lower levels may be sufficient for the protection of depression [65,66]. In an open naturalistic RCT allowing comedication, no relation between serum–lithium levels and outcome could be demonstrated [67].

From Evidence to Clinical Practice

Specific Points on Generalizability of Results from RCTs on Lithium

When applying efficacy results from RCTs to clinical practice, the study populations and the study designs must be taken into account.

Regarding RCTs on mania in general, it is unlikely that the most severely ill patients will be recruited [68]. In particular such an informal selection may occur in RCTs evaluating lithium, since for safety reasons participants must not be too ill to be able to cooperate on the measurement of serum–lithium. In this way the generalizabilty of study results is narrowed, but at the same time it is more accurate.

In maintenance RCTs, an unsystematic selection of patients insufficiently responding to prior lithium prophylaxis may constitute a problem in terms of generalizability. Also, it should be born in mind that the major study results are derived from patients with bipolar I disorder (or in the earlier studies from patients with a history of clear mania), implying that the results are not necessarily transferable to the whole bipolar spectrum. What broadens the generalizability of some long-term trial results on lithium in comparison with that of trial results on other agents is that recent positive study results can indeed be applied to bipolar patients independently of whether they have received and potentially responded to lithium acutely. Obviously, the results from the long-term RCTs can only be applied to populations with similar levels of compliance as those achieved under the trial conditions. However, the noncompliance rates observed under routine conditions in specialized settings may not differ much from the rates seen in RCTs. Thus, after 2 years observation, the noncompliance rates in two similar cohorts of bipolar patients beginning lithium prophylaxis and treated in large at the same specialized setting, one treated under routine conditions [69] and the other treated as part of an open RCT [54] were 49% and 31%, respectively. Accordingly, lithium has been demonstrated to be effective, albeit to a lesser extent than in RCTs, in observational studies monitoring patients treated in specialized settings under routine conditions [70]. The presence of comorbid disorders like substance abuse may contribute to a reduced effectiveness under such conditions.

Since the outcome measure in all recent long-term-RCTs is time to first relapse/recurrence, any continued treatment under routine conditions beyond this point literally is not evidence-based. However, lithium (and other drugs) may need time to work. Additionally, a prophylactic response may be partial, even this has not been systematically evaluated in RCTs.

RCTs in bipolar disorder generally include patients aged 18 and above, and only very few RCTs (and no long-term RCTs) on lithium have been conducted in children and adolescents [71–73]. However, in this population, lithium seems to have antimanic efficacy comparable to that seen in adults, at least in nonpsychotic mania. Also, there are observational studies indicating long-term benefits of long-term lithium treatment in certain subgroups of patients [74].

Lithium's Place in the Treatment of Bipolar Disorder

In the current guidelines, lithium is recommended as a first line monotherapy agent for the treatment of classical mania [27,75–80], in some guidelines only for the milder cases [76,77] and in the WFSBP guideline only if maintenance treatment is indicated [27]. All the guidelines include a combination of lithium and another antimanic agent as an option under various circumstances.

For acute bipolar depression, lithium is also considered a first line treatment in the current guidelines with one exception [77]. In the WFSBP guideline, lithium is given a relatively low recommendation grade of five due to the conflicting evidence [81].

However, given the few options for treating this condition, all drugs with recommendation grades 1–5 are considered first line options [81].

For maintenance, all guidelines state lithium as a first line treatment [75], with an additional consensus that lithium is the drug with the best evidence also for an antisuicidal efficacy. Two different strategies for the use of lithium as a first line agent in maintenance can be adopted. Either, lithium is considered the first drug of choice, a choice that may be waived for several reasons, for example, continuation of a successful acute treatment other than lithium, patient nonpreference, anticipated noncompliance or previous nonresponse, or lithium may be chosen on the basis of the clinical profile, that is, a positive family history of bipolar disorder, classical presentations of episodes, and most importantly, full interepisodic remission [82,83]. Additionally, lithium should obviously be considered for maintenance in cases where it has been used successfully for acute mania. Given the scarcity of RCTs on combining long-term lithium with other prophylactic agents, monotherpy is generally recommended as a starting point. However, a temporary continuation therapy with an agent other than lithium in combination with lithium is often relevant in the aftermath of the acute treatment of mania or depression. When lithium is not the first choice for maintenance, it may be added later, either sequentially or as an add-on.

Concerns on the Use of Lithium

Among the various adverse effects of lithium (Table 1) [4,10], the potential irreversible long-term renal side effects, albeit very rare, may be those of greatest concern for the clinician [84,85]. Also, the risk of CNS toxicity, which may lead to irreversible sequelae [86] is a point of concern. From the patient perspective, in addition to the just mentioned adverse effects, the risk of weight gain and the risk of psychic side effects (cognitive impairment and/or reduced intensity of perceptions and emotions) may be most crucial. Lithium's teratogenic effect hardly ever gives rise to not initiating lithium treatment, possible due to the fact that the risk is well characterized and relatively low in absolute terms [87].

Table 1 Adverse effects of lithium (therapeutic doses)

Common adverse effects (more than 10%)	Less common adverse effect (less than 10%)
Tremor[a]	Nausea[a]
Diarrhea[a]	Acne
Thirst[a]	Psoriasis
Polyuria[a]	Hypothyroidism
Weight gain	Cognitive impairment[a]
	Reduced emotional and/or perceptual intensity[a]
	Cardiac arrythmia
	Hyperparathyroidism
	Renal impairment[b]

[a]Dose related.
[b]Related to the total lithium exposure over time and to the occurrence of serum–lithium levels above the therapeutic range.

A potential risk of withdrawal mania beyond a simple relapse due to an early drug discontinuation has led to some concerns as regards the use of lithium for mania when future compliance cannot be anticipated [88]. However, if withdrawal mania is a true phenomenon, it may occur with other agents as well [89].

A Few Notes on Practical Management

Before lithium is given, as a minimum renal disease and major derangement of electrolytes must be excluded [80]. Additionally, renal function must be screened every 3 months during maintenance treatment through determinations of serum–creatinine, and even slight increases in the level must lead to proper actions. Due to lithium's low therapeutic index, serum–lithium levels must always be monitored during lithium treatment. Thus, the serum–lithium should be measured as a minimum when treatment is initiated, after any dose increase and during maintenance every 3 months. The blood samples for measuring the serum–lithium must be drawn at steady state in the morning, approximately 12 (or 24 h after the last dose is taken. This standardization is crucial for the evaluation of intra-individual changes over time. Moreover, to avoid toxicity, patients (and their relatives) must always be informed in detail about the symptoms and signs of toxicity and about risk situations (Table 2) [90].

Despite the recommended evidence-based ranges of serum–lithium reviewed above, the optimal serum–lithium varies across patients. This variation is due to interindividual differences in sensitivity to lithium and due to the fact that the ratio between the 12/24 h serum–lithium and the average serum–lithium varies across patients due to the interindividual variations in renal clearance [91]. The latter phenomenon explains why a young patient with a high renal clearance may have an unexpectedly low 12/24 h serum–lithium despite a relatively high daily lithium dose. Therefore, doses should also be adjusted according to effect and adverse effects.

Table 2 Symptoms and signs of lithium intoxication[a] and situations associated with an increased risk of intoxication

Symptoms and signs	Risk situations
Mild intoxication:	Lithium overdose
Cognitive impairment, lethargia, tremor dysartria, nausea	Increased loss of water and/or salt (e.g. gastrointestinal infection, increased sweating)
Moderate intoxication:	Decreased intake of water and/or salt (e.g. various disease states)
Disorientation, impaired gait, twitching of muscles, vomiting	Impaired renal elimination of lithium (renal disease, old age)
Severe intoxication:	Major surgery
Delirium, convulsions, ataxia, renal impairment	Concurrent treatment with thiazide diuretics and/or nonsteroidal antiinflammatory drugs

[a]May begin to appear with serum lithium levels above 1.2 mEq/L. However, intoxication is not incompatible with lower levels of serum–lithium since lithium is eliminated at a lower rate from the CNS than from the serum.

When lithium treatment has been used for mania and is to be continued for maintenance, doses should be reduced when the manic symptoms cease, not only because of the lower recommended serum–lithium for maintenance but also because of the state-dependent kinetics of lithium (with higher lithium clearance during mania) [4].

Steady-state is reached after 4–7 days (or more when the elimination half-life of lithium is increased). Lithium clearance is one-third to one quarter of the Glomerular Filtration Rate (GFR) and thus follows renal function. Accordingly, there is a constant ratio between the daily lithium dose and the steady-state serum–lithium level in an individual patient provided that the GFR and the level of hydration are unchanged.

Conclusions

By being able to reduce acute symptoms of mania and of bipolar depression, albeit the latter with some uncertainty, and by being able to prevent the recurrence of symptoms of either pole independently of any acute response, lithium can still be considered a major mood-stabilizing drug if not the mood-stabilizing drug par excellence. This is reflected by its position in current guidelines. It naturally also plays an important role that lithium is the cheapest mood-stabilizing drug. The potential risks of lithium should be weighed up against its benefits and the fact that serious adverse effects are most often avoidable, provided that skilled clinicians carry out the treatment taking all the necessary precautions.

Despite the well proven efficacy of lithium, there is indeed still room for improvement as regards the long-term treatment outcome of patients commenced on the drug for prophylaxis [92]; as stated by Cuscot and Taylor: "Its not lithium alone but the mode of service delivery which confers the benefit" [93].

Still much research is called for. An understanding of the specific mechanisms of lithium's antibipolar actions might substantially improve our knowledge on prediction of lithium response. Such an understanding might also lead to an understanding of the pathogenesis of bipolar disorder. There are international collaborative attempts to meet these goals through studying the potential genetic underpinnings of lithium response [94]. In the meantime, the conduct of RCTs on samples of various homogenous populations, also in younger age groups, might be a path to follow. Also, more studies on the management of patients not responding to lithium and the role of lithium in bipolar patients nonresponsive to other treatments would be clinically highly relevant. Finally, large-scale RCTs evaluating lithium in combination with other agents are warranted [95].

Conflict of Interest

In the last 3 years, the author has been in the advisory boards of Bristol-Myers Squibb, Astra-Zeneca and MSD and has received honoraria for lectures from Eli Lilly, Janssen-Cilag, GlaxoSmithKline, Bristol-Myers Squibb, Pfizer and Asrea-Zeneca.

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