Abstract
The fact that various drugs with different mechanisms of action can induce suicidality even in people who never had suicidal ideation before suggests that the neurobiological correlates of suicidal ideation and behavior are complex and not very well understood. Lithium and clozapine are unique substances since they are the only psychotropic compounds for which evidence of an antisuicidal effect exists so far. In this chapter the scientific proof for such effect will be unfolded in a narrative review. Particularly for lithium salts, this effect has been documented since the 90s in a large number of studies with quite different methodological approaches by various international research groups. It could be shown beyond any doubt that the 2- to 3-times elevated standardized mortality of patients with affective disorders can be reduced by a well-monitored lithium prophylaxis to the level of the general population. Various studies suggest that other ‘mood stabilizers’ do not possess this property, at least not to the same extent. Some authors based on their studies have concluded that this lithium effect might be specific, i.e. independent of lithium’s episode-preventing activity. Clozapine possesses antisuicidal and, similar to lithium, also antiaggressive effects and efficacy in schizophrenic patients, although the evidence is not as strong as with lithium, considering the smaller number of large studies. Clozapine also counteracts aggressive and self-mutilating behavior in patients with personality disorders. Possible neurobiological mechanisms underlying these unique effects of lithium and clozapine are discussed at the end of the chapter, for example changes in postsynaptic 5-HT_1A receptor activity might be a link between certain clinical effects of antidepressants, lithium and clozapine.

Various chapters of this book provide ample evidence that suicidal behavior can be caused by or rather is associated with not only psychosocial, spiritual, emotional, or cognitive but also biological factors per se. This becomes evident also from the...
longstanding observation that a large variety of drugs can induce depressive states, suicidal ideation and suicidal behavior. Among them we find pharmacologically quite different compounds such as, for example, interferon-α, mefloquine, isotretinoin, finasteride, fluoroquinolones, and quite surprisingly, even antidepressants, particularly SSRIs [1–4]. The underlying mechanisms are mostly unclear. For example, a potential negative influence on precursors of the serotonin metabolism has been discussed for interferon-α [5]. Glutamatergic and GABAergic mechanisms might play a role in the suicidogenic effects of finasteride. On a behavioral level, excitatory, anxiety-inducing effects have been made responsible for the suicide-provoking effects of SSRIs. Whether such effects would also be responsible for antidepressant-induced emergent suicidal ideation in patients who never before had shown any suicidal ideation or behavior, however, is unclear. Fortunately, only a small number of patients will develop suicidality triggered by antidepressants; children and adolescents appear to be at special risk. This implies that special unknown resilience factors preventing this side effect obviously must exist and that the mental and biological factors defining an individual proneness to suicidal thoughts and behavior might be different in adolescents and adults. Interestingly, some recent findings suggest a genetic predisposition for the occurrence of this occasionally fatal adverse drug reaction [6].

In contrast to the great number of compounds possessing depressogenic/suicidogenic properties, pharmaceutical agents that could effectively counteract suicidality or diminish an increased long-term risk of committing suicide are surprisingly rare. Only two compounds exist for which robust or at least satisfactory evidence of an antisuicidal efficacy exists in patients with affective disorders or schizophrenia – lithium salts and clozapine. Lithium’s very convincingly documented antisuicidal effects have become a strong argument of high ranking in recent guidelines to classify lithium as a unique first-choice agent for the long-term treatment of patients with bipolar disorders (e.g. Deutsche Gesellschaft für Bipolare Störungen/Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde, DGBS/DGPPN).

It appears particularly puzzling that antidepressants do not possess a specific antisuicidal effect. Clearly, in a case where suicidal ideation is embedded in an acute depressive state, an improvement of depression would also result in a reduction of the frequency and impact of suicidal thoughts. However, claims that antidepressants could reduce the inherent suicide risk in patients with affective disorders are not in accordance with the overall scientific evidence [7]. Thus, none of 6 meta-analyses comprising between 20,000 and 90,000 patients from published RCTs found a significant reduction of suicidal acts in the antidepressant versus the placebo groups. In the meta-analysis of Fergusson et al. [8], the rate of suicides and suicide attempts was even higher in the SSRI group compared to placebo. A recent reanalysis by Gibbons et al. [9] referring only to fluoxetine and venlafaxine also clearly shows that in adults the development of suicidal acts and overall suicidal ideation over time does not differ between the antidepressant and the placebo group.
Lithium

In the following we do not intend to provide the reader with a comprehensive overview on the existing studies in this area [10]. Rather, we are going to document the existence of the antisuicidal effects of lithium and clozapine, referring to a selection of representative and valid studies and also reviews in this area. This will also include a discussion of the data suggesting the antisuicidal/antiaggressive efficacy of lithium as a trace element in large epidemiological studies. We shall outline in short the history and development of international research on the suicide-preventive effect of lithium. We then discuss the potential specificity of the antisuicidal effect, focusing on the following important questions: (1) whether the suicide- and mortality-reducing effect of lithium is shared by other psychotropics including mood stabilizers and (2) whether this effect might be independent of the episode-suppressing effect.

Can Adequate Lithium Prophylaxis Change the Suicide Risk and Mortality of Patients with Affective Disorders?

Patients with affective disorders exhibit a 2- to 3-times increased mortality compared to the general population [11, 12]. This excess mortality is caused primarily by the possibly 30- to 70-fold higher suicide-related mortality [13] – which is particularly high in patients with a history of suicide attempt [14, 15]. The meta-analysis by Guze and Robins [16] calculated the lifetime suicide risk as 15% for affective disorders, whereas 20 years later Goodwin and Jamison [17] – based on more recent literature – reported an overall risk of 19%. According to the WHO [18] the lifetime risk ranges between 6 and 15%. According to a recent review the lifetime risk of suicide in patients with mood disorders is 5–6%, with possibly a higher risk in patients with bipolar disorders [19].

As reported by Harris and Barraclough [20], the suicide-related standardized mortality ratio (SMR) is 21.24 in major depression and 11.73 in bipolar disorder, with, however, large confidence intervals [21].

The intriguing question of whether long-term medication with lithium salts can improve the course of the manic depressive illness or of affective disorders in terms of suicide prevention has been given little attention up to the 80s (table 1).

Barraclough [22] was one of the first investigators postulating a potential association between lithium long-term medication and suicide prevention. Based on a detailed analysis of the charts of 100 suicide victims he concluded that about 20% of the suicides could have been prevented by adequate lithium medication. The first systematic retrospective study demonstrating a highly significant reduction of suicide attempts in a sample of 64 high-risk patients (46 bipolar and 11 schizoaffective) during long-term lithium treatment was published by Müller-Oerlinghausen et al. [23]. The authors emphasized that suicides and suicide attempts occurred nearly
Felber and Kyber [24] in Dresden analyzed suicide attempts during accumulated periods on and off lithium and had very similar findings – 90% of the suicide attempts occurred in the off-lithium period.

Several studies on the mortality of affective disorders during lithium long-term treatment by Coppen et al. [25] and Ahrens and Müller-Oerlinghausen [26] demonstrated that the SMR of patients with affective disorders during adequate lithium medication is normalized down to the level of the general population. Coppen [27] reviewed the studies existing in the mid-90s on the suicide rates in patients on versus off lithium and concluded that adequate lithium medication reduces suicide-related mortality by 82%.

### Table 1. Antisuicidal effect of lithium: history

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Anecdotal reports and findings from follow-ups in the 70s and 80s on possible reduction of suicidal behavior in lithium-treated patients

First systematic follow-up studies of high-risk patients during long-term lithium treatment

Berlin study: 2 suicides, 4 suicide attempts in 55 patients with regular lithium treatment; 4 suicides, 7 suicide attempts in 13 patients having discontinued lithium

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The IGSLI Studies

In the main study of the IGSLI (International Group for The Study of Lithium-Treated Patients) well-documented data on the course of illness of 827 patients with affective disorders from lithium clinics in Austria, Canada, Denmark, and Germany who had been treated with lithium for at least 6 months were evaluated – 55% of the patients were bipolar, 25% unipolar, 2% unipolar-manic, 16% schizoaffective, and 2% had other diagnoses [21, 28]. At the onset of the lithium prophylaxis the patients were on average 41 years old. The mean duration of lithium treatment was 81 months (6–21 years), equaling 5,600 patient-years.

The ratio of 44 observed and 38 expected cases of death is not statistically different from 1.0, which is the mortality of the general population. Thus, the expected 2- to 3-fold excess mortality in patients with affective disorders (see above) did not exist in this lithium-treated patient sample. Bipolar patients do not differ essentially from other diagnostic groups in this respect.

Although the specific suicide-related SMR was still higher than in the general population it could clearly be shown that it was definitely lower in all diagnostic groups compared to what could be expected in untreated patient samples.

It has been argued on various occasions that patients accepting a lithium prophylaxis might generally benefit from a better prognosis. In this case the specific patient selection would have been primarily responsible for the normalization of the SMR. To study this issue, in a successive analysis of 270 German and Danish patients from the original IGSLI sample the initial SMR was compared to the SMR after treatment of more than 1 year [29]. During the first year the overall mortality was increased 2-fold and the suicide-related mortality 17-fold compared to the general population. The SMR normalized after the first year of treatment, indicating that patients for whom lithium prophylaxis is indicated are in fact patients with a high risk of suicide.

Confirmatory data came from Italy when Bocchetta et al. [30] demonstrated a 6-fold decreased incidence of suicide attempts in 100 carefully monitored and documented lithium patients. During the observational period of approximately 10 years, 10 suicides occurred in this cohort – 9 of them in patients having discontinued their lithium medication. A year later a well-known research group in Boston (USA) also showed in a cohort of 300 bipolar patients that the incidence of suicide increased 20-fold in the first year after ending foregoing lithium medication [31].

Further Studies on Mortality

As mentioned above it was also argued that the reduction of mortality might essentially be due to the optimal care and attention patients receive in specialized lithium clinics. In this context 2 Swedish studies are of particular interest. In an open-field setting Nilsson [32] could not observe a full normalization of the SMR. However, as in other studies, Schou [33] found a rise of the SMR up to the expected level in untreated affective disorders after the discontinuation of lithium.
Kallner et al. [34] analyzed a mixed sample of 497 Swedish patients including 405 bipolar patients treated with lithium during an observation period of 30 years. The patients were divided into three groups according to the regularity of attending the study clinic. Among the bipolar patients the suicide rate was in excess in all three groups. However, the suicide rate was increased by 80% when patients stopped taking lithium. This study deserves special attention because on one side it generally confirms the findings by the IGSLI and by Nilsson but it also suggests that the suicide-preventing effect of lithium might be more marked in patients being taken care of in specialized lithium clinics. The suicide-related SMR in patients on lithium was 14.0 when they had regular visits to the clinic and 21.4 when treated elsewhere. This difference could possibly be explained by the generally higher quality of the treatment regimens and by the closer monitoring of the patients.

In 2005 Angst et al. [35] published a study of 406 patients with affective disorders who had been followed up over 40 years (the so-called Zurich cohort). The patients treated with lithium had a lower than expected mortality rate which was not different from the mortality rate of the general population.

There are very few studies apparently contradicting the findings of the IGSLI. Thus, Vestergaard and Aagaard [36] and Brodersen et al. [37] were not able to demonstrate reduced mortality in cohorts of lithium-treated manic-depressive patients. However, the average duration of the lithium treatment was less than in the IGSLI study and control of compliance might not have been sufficient – one third of the deaths that occurred in their study took place after patients discontinued lithium. Another negative though very small study was published by Coryell et al. [38].

Reviews and Meta-Analyses
The first meta-analysis on about 17,000 bipolar patients was published by the Boston group in 1997 [39]. It demonstrated an 8.6-fold higher mortality from suicide in patients treated without lithium than in patients during lithium long-term treatment.

Cipriani et al. [40] from Oxford meta-analyzed RCTs on the episode-preventive efficacy of lithium and found a very clear and highly significant reduction of suicidal acts and mortality for lithium compared to either placebo or any other psychotropics, including antidepressants. An updated version of this analysis was published by the same authors in 2013 [41]. The meta-analysis by Baldessarini et al. [42] published in 2006 referred to 33,000 patients and 45 studies and also proved that lithium-treated patients had a 5-fold decreased risk for suicidal acts and reduced overall mortality compared to patients having been given other medication.

An RCT to Explore the Suicide-Protective Effect of Lithium
There are many methodological obstacles to perform controlled prospective trials in the area of suicidology. First, the study protocol will usually exclude patients with suicidal tendencies from drug trials. Second, from an ethical point of view, placebo-
controlled studies with suicide or suicide attempt as primary outcome will hardly be acceptable. Third – since suicide is fortunately a relatively rare event – large patient numbers would be needed to reach sufficient statistical power, resulting in a nearly unsolvable ethical dilemma. Nevertheless, an independently sponsored RCT from Germany, which due to the above-mentioned and additional methodological difficulties could not be performed in full concordance with the requirements of the power calculation, had an interesting and confirmatory result. Within the treatment period of 1 year no suicides occurred in the lithium group (n = 84), whereas 3 suicides occurred in the placebo group (n = 84) [43]. Interestingly, a post hoc analysis did not show a suicide-protective effect in those patients of the study who had also been given a diagnosis of personality disorder [44].

Is the Anti-Suicidal and Mortality-Reducing Effect of Lithium Specific?
In view of these rather robust and consistent findings the intriguing question arises whether the suicide-preventive effect of lithium should be considered a ‘specific’ effect – and what could be the underlying mechanism?

For the sake of clarity we may subdivide the issue of potential specificity into two questions, as follows:
1. Is this effect specific for lithium salts – in other words, is it not shared by other drugs such as other mood stabilizers or antidepressants?
2. Is this effect strictly related to the episode-preventive effect of lithium prophylaxis or might it act independently?

The question of whether the antisuicidal effect is shared by other psychotropic agents was addressed in the German multicenter MAP study – a prospective RCT with a treatment time of 2.5 years. In total, 146 bipolar and schizoaffective patients were randomized on lithium and 139 on carbamazepine. No suicidal act was observed in the lithium group. However, 4 suicides and 5 suicide attempts occurred in the carbamazepine group – a statistically significant difference [45–47].

A study by Goodwin et al. [48] comparing the suicide risk in lithium- versus valproate-treated patients has found much attention in the USA. The authors conducted a retrospective cohort study on two large integrated health plans in California and Washington. In this follow-up of more than 20,000 patients who received lithium, carbamazepine or valproate between 1994 and 2001 the adjusted suicide risk was 2.7 times (95% CI 1.1–6.3; p = 0.03) higher in the valproate-treated patients compared to the lithium-treated patients. Hazard ratios for suicide attempts amounted to 1.7–1.8. In addition, the carbamazepine-treated patients had a significantly higher risk of suicide attempts leading to hospitalization in comparison to patients having been prescribed lithium at least once during the observation period.

Collins and McFarland [49] investigated 12,626 Medicaid-insured patients and demonstrated that lithium-treated bipolar patients had the lowest number of suicide attempts compared to those having been prescribed other mood stabilizers.
Oquendo et al. [50] observed the effect of lithium compared to valproate in the prevention of suicidal behavior in patients with bipolar disorder over a period of 2.5 years. During that randomized clinical trial no suicides occurred within the whole study sample. Overall, 6 suicide attempts were registered in the lithium group (n = 49) and 8 in the valproate group (n = 49). Unfortunately, due to a high attrition rate, the study lost considerable statistical power. In this context it might also be worth mentioning that in the RCT by Lauterbach et al. [43] only the incidence of suicides, but not of suicide attempts, differed between the lithium and the placebo group.

In a large study by Weisler et al. [51] comparing the effect of prolonged quetiapine medication versus switching to placebo or lithium for maintenance treatment in 2,438 bipolar I patients, only 1 suicidal/accidental gunshot wound was observed during the open-label treatment with quetiapine. During the randomized phase only a low and similar overall incidence of suicidal behavior/ideation was observed in the quetiapine (n = 3), lithium (n = 3) and placebo (n = 8) groups.

Khan et al. [52] published a study primarily designed to investigate whether the antisuicidal effects of lithium can be prospectively evaluated using lithium as an augmenting agent to antidepressants. A subgroup of the patients assigned to citalopram and lithium achieved therapeutic serum levels and had significantly higher S-STS (Sheehan Suicidality Tracking Scale) remission rates compared to patients assigned to citalopram or placebo alone. They debated that lithium when used in therapeutic doses may augment a direct therapeutic effect of citalopram on suicidal thoughts and behavior.

Taken together, some studies suggest that a few nonlithium compounds might protect patients with mood disorders against suicidal acts to some extent. Such potential and possibly only modest effects, however, can hardly be documented in a study cohort showing only a low suicide risk.

**What Could Be the Mechanism of This Suicide-Preventive Effect?**

While it was postulated by Baldessarini et al. [53] that the reduction of the suicide risk by lithium prophylaxis is primarily caused by its depression-preventive effect, the hypothesis of the Berlin group from the very beginning has always been that lithium differs from other mood stabilizers and also from most antidepressants by its very marked serotonin agonistic effects which are related predominantly to its presynaptic functions [54, 55]. It appears to be at least an attractive speculation that this serotonergic action of lithium, possibly in connection with other effects, is related to its very well-established antiaggressive effects in animals as well as humans [56, 57] but also to its antisuicidal effects. In one of the rare animal studies focusing on potential neurobiological underpinnings of the clinical effects of lithium, Ohmura et al. [58] investigated whether major mood-stabilizing drugs used for the treatment of bipolar disorder could suppress impulsive-like action in the three-choice serial reaction time task in rats. The authors debated that lithium, but not valproate or carbamazepine, may suppress impulsive behavior and thereby decrease the risk of suicide. Shock-
induced aggression in mice is also attenuated by lithium, as shown by Kovacsics and Gould [59]. Overall, neurobiological research has focused on lithium’s influence on neurotransmitters such as serotonin, noradrenalin and dopamine, the cortisol stress hormone system, the γ-aminobutyric-acid, second-messenger systems such as inositol metabolism, glycogen synthase kinase 3, and more. The most favored hypothesis is that lithium leads to a decrease of impulsivity and aggression via several influences within the nerve cell [57, 60]. The neurobiological research on suicide at present points to an important influence of overactivity of the corticotropin-releasing hormone, as well as of the noradrenergic system, and a dysfunction of the serotonergic system [61, 62]. There could be a link between these dysfunctions and microglial hyperactivity. Thus, quinolinic acid derived from tryptophan could lead to a lowered cerebral level of tryptophan and serotonin [63]. Could it be that lithium by its serotonin agonistic properties counteracts this deficiency on the neurotransmitter level?

We may also approach the problem from another side, i.e. considering the endophenotype of a suicidal individual [64]. Some findings suggest that suicidal behavior might be seen as a particular, possibly anger-related form of affective dysregulation that is also associated with disturbance of the serotonin (5-HT) system and, thus, as a more or less independent nosological syndrome. Therefore, according to data from the WHO study from the year 2000 the prevalence of suicidal ideation and behavior is not fully related to the existence of ICD psychiatric diagnoses but it occurs frequently in symptomatic individuals and in subjects with subthreshold disorders [65]. Many such people are characterized by symptoms of overt or suppressed anger [66] which van Praag [67] considers as one of the core constituents of the stress syndrome, together with anxiety. He postulated that in certain types of depression – characterized by a 5-HT disturbance – anxiety and aggression regulation are primarily disturbed, while mood lowering is a derivative symptom. Consequently, he expected that certain drugs such as L-tryptophan, the azapirones or lithium might ameliorate anxiety and/or aggression regulation via the regulation of the 5-HT system to exert, in addition, an overall therapeutic effect in depression. Supposing van Praag’s concept would hold true, speculation that lithium might also possess acute antisuicidal properties appears warranted. A recently approved clinical project at the Department of Psychiatry, University of Dresden, will address this pressing question [68].

It is unfortunate that only few experimental psychologists tried to integrate the clinical effects of lithium into psychological constructs of experience and behavior as well as of cognition. Thus, some experimental approaches of the Berlin group, including the backward masking technique, and refined EEG studies point to a lithium-induced restricted number of degrees of freedom in neuropsychological/neurophysiological terms which might be related to a shorter persistence of external and internal stimuli. Such effects of long-term lithium medication might also fit to the observation derived from memory experiments in healthy volunteers that short-term administration of lithium modifies (diminishes) spontaneous initial action or, in other words, the will to act [69–73].
The second intriguing question associated with the issue of specificity is whether the antisuicidal effect of lithium would also occur in patients not responding optimally in terms of episode prevention. Part of the IGSLI data does in fact support such a concept. Addressing this issue, Ahrens and Müller-Oerlinghausen [74] selected only patients with at least 1 suicide attempt in the past before the onset of lithium medication (n = 176; 55% bipolar, 18% schizoaffective). The sample was divided into three subgroups according to their response to lithium long-term treatment in terms of reduction of depressive inpatient episodes. Despite the clearly different overall efficacy of lithium prophylaxis a statistically significant reduction of suicide attempts occurred in all three groups, even in the poor responders who did not show a significant decrease in the depressive inpatient episodes. In other words, in 50% of the clear-cut nonresponders no further suicide attempt was observed during lithium treatment.

The standardized suicide mortality in the poor responders was 17.0 compared to an expected figure of approximately 100. Certainly, these findings can neither prove the suicide-preventive effect of lithium nor its potential specificity. However, the accumulated evidence strongly supports such a possibility.

Studies on Potential Antisuicidal Effects of Lithium as a Trace Element in Drinking Water

Much scientific and media attention has been raised by recent epidemiological studies hinting at the possibility that even extremely low amounts of lithium could exert antisuicidal and antiaggressive effects. There exist at present 5 studies – 4 positive and 1 negative – linking lithium levels in drinking water to suicide rates in various countries and regions. Of these, 2 studies, 1 from Japan [75] and the other from Austria [76, 77], concluded that areas with higher lithium levels in the drinking water had lower suicide rates. A Greek study by Giotakos et al. [78] confirmed these results, as the authors found a tendency for lower suicide rates in the prefectures with high levels of lithium in drinking water. Blüml et al. [79] also showed in a state-wide sample of 3,123 lithium measurements in the public water supply of Texas that lithium levels were negatively associated with suicide rates in most statistical analyses.

A study by Kabacs et al. [80] measuring lithium levels in tap water in 47 subdivisions of the East of England and correlating these with the respective suicide SMR in each subdivision did not show an association between lithium level in drinking water and suicide rates.

Very recently, these studies were summarized and reviewed by Vita et al. [81]. The authors conclude that ‘these studies are surprisingly consistent in demonstrating a highly significant correlation between lithium levels in drinking water and suicide rates’.

To the knowledge of the authors, so far no pharmacological or biochemical findings exist which could be attributed to these fascinating and provocative findings, the interpretation of which, however, has to consider the usual pitfalls of any epidemiological data.
The Efficiency of Lithium Prophylaxis in Terms of Saved Lives

In 2004, Joffe [82] posed the question in an editorial: ‘Does lithium save lives?’ Ahrens and Müller-Oerlinghausen [83] developed a model for the calculation of deaths and suicides to be expected in the general population and in untreated patients with affective disorders. Based on their calculation they concluded that 5 suicides per year and 1,000 treated patients can be prevented. This would result in approximately 250 suicides per year prevented in Germany. The IGSLI data also shows that the average age of patients having committed suicide was 44. Thus, the gain for the gross national product in Germany would be 3,060 working years before completing the age of 65.

Clozapine

Clozapine Counteracts Suicidality and Aggressive Behavior in Patients with Schizophrenia and Borderline Personality Disorder

The risk of suicide exists not only in patients with mood disorders but also in those with a diagnosis of schizophrenia and schizoaffective and borderline personality disorders (BPD). It is said that suicide accounts for approximately 10% of deaths in patients with schizophrenia [84–86]. About one third will attempt suicide at least once in their life. Various clinical trials have shown that clozapine is unique among all antipsychotic agents as it can reduce positive as well as negative symptoms in schizophrenic patients not responding to any other typical or atypical neuroleptic medication. According to the recent guideline of the European Psychiatric Association on suicide prevention treatment clozapine is also effective in reducing suicidal behavior in schizophrenic patients [87]. Corresponding evidence appears to be much weaker for any other ‘atypical’ antipsychotics such as olanzapine, risperidone or quetiapine.

Besides many case reports, there exist also some controlled prospective studies which have been summarized by Aguilar and Siris [86] and Kerwin and Bolonna [85]. A prospective but noncontrolled study by Meltzer and Okayli [88] as well as a retrospective study by Walker et al. [89] have already provided a strong suggestion that clozapine can dramatically reduce the number of suicides and suicide attempts. A large independent multicenter, international RCT on 980 patients over 2 years (the International Suicide Prevention Trial Study in collaboration with the FDA) could then clearly demonstrate that clozapine was about 25% superior to olanzapine in preventing suicidal acts [90].

Already in 1998, Meltzer [84] recommended from the then existing evidence that clozapine should not only be prescribed to antipsychotic drug nonresponders but also to responders showing persistent suicidal thoughts and behavior – which would actually be an off-label use of this compound.

Clozapine did not show special superiority in antisuicidal activity among a group of atypical antipsychotics including olanzapine, risperidone or ziprasidone within a
recently published nested case-control study from Sweden [91]. Interestingly, the authors could not identify any antisuicidal activity for antipsychotic depot injections nor for antidepressants or lithium administered to 4,000 schizophrenic and schizoaffective patients, including 84 patients who died by suicide within 5 years of diagnosis.

_Treatment of Aggressive and Self-Mutilating Behavior in Patients with Borderline Personality Disorder_

Suicidal, self-mutilating and aggressive behavior often poses serious problems in the care of patients with BPD. According to Paris and Zweig-Frank [92] approximately 10% of patients with BPD die from suicide. A multitude of case reports in the past have suggested that clozapine acts very favorably in such patients since it reduces self-injurious as well as open aggressive behavior. Zarzar and McEvoy [93] support the existing evidence by adding 4 very impressive cases of BPD patients having been admitted, often repeatedly, to a state hospital. All of them received clozapine (with blood levels ranging between 161 and 312 ng/ml). The striking and obvious results of the medication were as follows: (1) the reduction of self-injurious behavior appeared in a short time, i.e. within 2 weeks, (2) patients reported a ‘marked reduction in misery’ and (3) the need of restrictive measures (restraining, 1:1 observation) could be reduced mostly within a few weeks.

As mentioned above, a general more or less unique antipsychotic effectiveness of clozapine which also possesses antidepressant activity is observed when it comes to the treatment of schizophrenic patients unresponsive to medication with other antipsychotics. Thus, neurobiological findings suggesting specific pharmacological properties in which clozapine differs from other antipsychotics might perhaps provide some clues to the mechanism of the antisuicidal effect of lithium. In this context it appears to be of interest that on one side the activation of postsynaptic 5-HT$_{1A}$ receptors in corticolimbic areas seems to be associated with the therapeutic effects of antidepressants, while on the other side characteristics of the postsynaptic receptors in the prefrontal cortex might be related to the unique properties of clozapine [94]. Clozapine is said to exert functional agonistic effects on these receptors in vivo, possibly resulting in increased dopamine release in the prefrontal cortex via activation of the mesocortical pathway. It has been speculated that this effect could be seen as a biological correlate to its beneficial effect on negative symptoms and cognitive deficits in chronic schizophrenic patients. Lithium, on the other hand, has also been shown to enhance 5-HT$_{1A}$ receptor function, whereas chronic stress reduces the gene expression of these receptors in experimental animals. Increased 5-HT$_{1A}$ receptor binding in the hippocampus and amygdala has also been shown in humans having been exposed to lithium medication [95].
References

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