Neurobiological Evidence for the Antisuicidal Effect of Lithium: A brief review

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To date, numerous studies have examined the effect of lithium on clinical manifestations of the spectrum of suicidal behavior. However, their findings remain to be incorporated as recommendations in current clinical guidelines. This review of major studies, reviews and meta-analyses summarizes the principal findings regarding lithium's antisuicidal properties, from clinical reports to neurobiological studies. A pathophysiological model of the antisuicidal effect of lithium is proposed, integrating clinical and neurobiological findings. In conclusion, there is strong evidence of neurobiological underpinnings supporting an antisuicidal effect of lithium. Some derived clinical recommendations are discussed.

Introduction

The introduction of lithium as a treatment for mania in 1949 (Cade, 1949) has been referred to as “the beginning of modern clinical psychopharmacology” (Rybakowski, 2010). Lithium's antisuicidal properties were first hypothesized (Barracough, 1972) based on observation of its prophylactic effect in recurrent affective disorders (Angst et al., 1970), (Coppin et al., 1971). Since then, numerous studies have examined the effect of lithium on clinical manifestations of the spectrum of suicidal behavior. However, the resulting body of knowledge has not translated into unanimous recommendations in current clinical guidelines.

This review summarizes major findings concerning the neurobiological evidence of lithium's antisuicidal effect and discusses how that evidence can be incorporated into clinical practice. Studies reviewed herein do not include every published study focused on the putative antisuicidal effects of lithium; rather, we have reviewed the major studies, reviews and meta-analyses in the literature. While the main indication for lithium remains the long-term treatment of bipolar disorder (BPD), its capacity to lower suicide risk has been studied in the broader spectrum of major affective disorders (MADs), both for methodological reasons and because of what has been described as a continuum between recurrent unipolar depression and BPD (Cassano et al., 2004). Therefore this review is not limited to published results on bipolar disorder exclusively.

Method

A computer-assisted search of the PUBMED database was conducted with

the keywords 'lithium' and 'suicide', including related terms. In a second step, the same search was restricted to titles, followed by a review of selected bibliographies done by hand. Given the large number of articles that were initially identified, a selection was implemented according to the authors' criteria. These criteria were, for clinical studies, those in which an estimation of the risk of suicide behavior or of mortality is provided, and for neurobiological studies, those focused in the antisuicidal properties of lithium.

Clinical evidence of the antisuicidal effect of lithium

Overview of the magnitude of the clinical effect

The association of long-term lithium treatment of affective disorders with reduced suicide risk is supported by numerous studies, most of which have been included in several reviews and meta-analyses published over the past 15 years (Table 1).

Studies on suicide risk in BPD show a decrease in suicide rates over time, from a mean lifetime rate of 19% in a review of early studies (Goodwin & Jamison, 1990) to more recent estimates of around 5% among cases of milder severity (for a review see (Tondo et al., 2003)). The introduction of lithium in the treatment of BPD has been proposed as one major reason for this decrease (Goodwin & Jamison, 2007).

Reviews and meta-analyses published to date are largely concordant in showing an association between lithium treatment and a significant reduction of both suicide and suicide attempt (Baldessarini et al., 2003), (Cipriani et al., 2005), with risks ratios of 3.97 and 4.74 respectively,

(Baldessarini et al., 2006), (Baldessarini & Tondo, 2008). This translates into a 7-fold to 13-fold reduction of the risk of suicide (Tondo et al., 1997), (Tondo & Baldessarini, 2000), (Tondo et al., 2001), (Baldessarini et al., 2001) and a significant reduction of the overall mortality in these disorders, with the protective influence of lithium being more evident in affective syndromes characterized by more depressive episodes or symptoms (Baldessarini et al., 2003). The resulting overall mortality rates reach a level only moderately higher than those of the general population (Schou, 1998), (Schou, 2000), (Müller-Oerlinghausen et al., 2005).

That only about 10% of all suicides among lithium-treated patients (Isometsa et al., 1992) use lithium as a lethal method has been hypothesized to be a direct consequence of its antisuicidal effect (Baldessarini et al., 2006), (Guzzetta et al., 2007).

Discontinuation studies

Discontinuation of lithium is associated with an estimated 7-fold increase in suicidal acts, a risk that is greater still during the first year when it is estimated to be 16- to 20-fold (Tondo et al., 1997), (Baldessarini et al., 1999). A higher relative risk of suicide (Kallner et al., 2000), of nearly 5-fold is also reported (Nilsson, 1995). This phenomenon reinforces the naturalistic observation that the majority of mood disordered suicide victims who were treated with lithium were actually non-adherent to treatment (Isometsa et al., 1992), (Bocchetta et al., 1998). Interestingly, this sharp increase in suicide risk after lithium discontinuation also occurs in patients whose mood symptoms had not responded to lithium,

Table 1:

Study	Year	Type of study	Studies and sample covered	Risk type (years)	Main conclusions on the antisuicidal effect of long-term lithium maintenance
Tondo et al.	1997	Review	28 studies, over 17,000 patients with MAD	S, A	8.6-fold ↓ in suicidal risk with vs without lithium treatment 7-fold ↑ of suicidal acts after lithium discontinuation
Schou	1998	Review	18 studies, over 2,000 patients with MAD followed on and off lithium, over 11,000 patient-years on lithium	SMR, S, A	- ↓ of overall mortality of patients in lithium treatment to the level of general population - Significant ↑ of mortality after discontinuation of lithium - Significant ↓ in suicidal risk with vs without lithium treatm.
Coppen	2000	Review	11 study (among others) of 103 patients with MAD (69 with unipolar depression) treated with lithium, followed during 18 years	S, Deaths	- Decreased suicide-related SMR vs the expected in untreated patient samples
Tondo and Baldessarini	2000	Review	22 studies, over 16,000 patients with MAD	S, A	7-fold ↓ in suicidal risk with vs without long-term lithium treatment
Baldessarini et al.	2001	Review and meta-analysis	33 studies nearly 14,000 patients with MAD	S, A	13-fold ↓ in suicidal risk with vs without long-term lithium treatment
Tondo et al.	2001	Meta-analysis	322 studies, 5647 patients (33473 patient-years)	S	Suicide 82% (5.50 times) less frequent with vs without lithium treatment. RR 8.85 (95% CI, 4.12–19.1)
Baldessarini et al.	2003	Review and meta-analysis	34 studies. 16221 patients, 64,233 patient-years	S, A	- Suicide 82% (5.43-fold) and A 93% (14.9-fold) less frequent with vs without lithium treatment - Risk percent ↓ by groups: UD (100%), BDII (82%), BDI (67%)
Cipriani et al.	2005	Systematic review and meta-analysis	32 RCT, 1,389 patients with MAD assigned to lithium vs 2,069 to placebo or other compounds	S, deliberate self-harm (incl. A), Deaths	- Lithium treatment associated with lower probabilities of: - Suicide (OR=0.26; 95% CI=0.09–0.77) - Composite measure of suicide plus deliberate self-harm lower in (OR=0.21; 95% CI=0.08–0.50) - Overall death OR=0.42, 95% CI=0.21–0.87
Müller-Oerlinghausen	2005	Review	IGSLI Studies (among others): 827 patients with MAD treated with lithium, 5,600 patient-years	S, Deaths	- Similar mortality to the expected in the general population - Decreased suicide-related SMR vs the expected in untreated patient samples
Guzzetta et al.	2007	Review and meta-analysis	8 studies, 329 patients with MDD, 1149 patient-years with and 1285 patients years without lithium	S, A	Overall risk 88.5% and suicide risk 85% lower with vs without lithium treatment
Baldessarini et al.	2006 & 2008	Review and meta-analysis	34 studies, of patients with MAD, over 85,229 patient-years,	S, A	S and A about 5 times less frequent with vs without lithium treatment, overall RR 4.14 (95% CI, 3.02–5.67) - For S: RR 3.97 (95% CI, 2.65–5.93) - For A: RR 4.74 (95% CI, 2.97–7.58)

A: Suicide attempts

IGSLI: International Group for the Study of Lithium-treated Patients (ref. Ahrens, Müller-Oerlinghausen, Schou et al., 1995; Müller-Oerlinghausen, Ahrens, Grof et al., 1992)

MAD: Major affective disorders

MDD: Major depressive disorders

OR: Odds Ratio

RCT: randomized controlled trials

RR: Risk ratio

S: Completed suicides

SMR: Standardized mortality ratio

UD: Unipolar depressive disorder

↓: reduction; ↑: increase

suggesting that any antisuicidal effect is independent of any effects on mood (Müller-Oerlinghausen et al., 1992), (Bocchetta et al., 1998). This observation has been proposed as an indicator of a specific antisuicidal effect of lithium and has been claimed to have practical clinical connotations.

A proposed pathophysiological model of the antisuicidal effect of lithium: integration of the neurobiological and clinical evidence

The neurobiological basis for the antisuicidal effects of lithium remains unknown. However, integration of (1) findings regarding the mechanism of lithium's action; (2) the clinical evidence described above; and (3) what is known about the neurobiological underpinnings of suicidal behavior (for review, see (Mann, 2003)) suggests a possible pathophysiological model. This model views impulsivity and aggression as major factors in suicidal behavior, putatively caused by low serotonergic function and a dysfunction of the inverse relationship between the prefrontal cortical and amygdalar activity in the regulation of emotions, aggression and impulsivity (Figure 1). Such a model is congruent with the neurobiological underpinnings of impulsive aggression: insufficient serotonergic facilitation of "top-down" regulation by prefrontal and anterior cingulate cortices of an excessive "bottom-up drive" to aggressive action, originating from hyperactivity of the amygdala and other limbic regions in the processing of emotional stimuli (Siever, 2008). Overall, three general mechanisms of action have been proposed for the antisuicidal effect of lithium.

a) Incidental to mood stabilizing

Considering both lithium's known properties as a mood stabilizer (Coryell, 2009) and the association between suicidal acts and recurrence of depressive or dysphoric-mixed episodes in BPD (Baldessarini et al., 1999), antisuicidal effects of lithium have been hypothesized to be a consequence of its capacity to reduce such recurrence (Baldessarini et al., 2001).

This proposal would be reinforced by evidence that the suicide-risk reduction provided by lithium is higher in affective syndromes mainly involving a depressive component (Baldessarini et al., 2003). However, Müller-Oerlinghausen's observation that lithium's antisuicidal effect is unrelated to mood stabilization weakens this formulation.

b) Potentiation of 5-HT in the forebrain -anti-aggressive and anti-impulsivity effect

Hypothesis of a specific serotonergic antisuicidal effect of lithium, independent of its mood stabilizing effect, first arose from the integration of neurobiological and clinical evidence. The former included discoveries of increased 5-HT₂ receptors in the frontal cortex of suicide victims (Stanley & Mann, 1983) and a brain pro-serotonergic effect of chronic lithium administration in animal and early human experimentation (Müller-Oerlinghausen, 1985). The latter came from evidence of lithium's anti-aggressive effects (M. Sheard, 1971), (M. H. Sheard, 1975), (Wickham & Reed, 1987) as well as anti-suicidal effects even in the absence of mood-stabilization (Müller-Oerlinghausen et al., 1992), (Ahrens & Müller-Oerlinghausen, 2001). Evidence for this mechanism of action also includes the association of suicidal behavior with aggression and impulsivity (Mann et al., 1999), a link which itself involves low serotonergic function (Mann, 2003).

An understanding of the mechanism underlying lithium's pro-serotonergic effects is still evolving. It may be related to 5-HT₂ receptors, resulting from the complementary and opposing role of 5-HT_{2A} and 5-HT_{2C} receptors in their modulation of impulsive aggression (for review, see (Siever, 2008)), (Terao, 2008). On the one hand, acute tryptophan depletion, a method that decreases serotonergic availability in the very short term, does not increase suicidality nor worsen affective symptoms in bipolar or unipolar depressed patients stabilized on lithium. It has therefore been suggested that the pro-serotonergic effect of lithium might be achieved via down-stream effects of 5-HT₂ receptors on other mechanisms

(Hughes et al., 2000), (Johnson et al., 2001). On the other hand, a positive relationship has been found between lifetime history of aggression and 5-HT_{2A} binding in prefrontal areas of suicidal subjects (Oquendo et al., 2006), and decreased 5-HT_{2C} receptor sensitivity may increase impulsivity. In support of this formulation, 5-HT_{2A} receptor antagonists and 5-HT_{2C} receptor agonists have been shown to reduce impulsivity (Siever, 2008).

These inverse effects on impulsivity caused by stimulation of the mentioned serotonin receptors show that this postulated pro-serotonergic effect of lithium is congruent with mechanisms of action proposed for SSRIs and clozapine, shown in some studies to decrease suicidal behavior (Hall, 2006), (Meltzer et al., 2003). Concerning SSRIs, paroxetine has been reported to downregulate 5-HT_{2A} receptors in young depressed patients (Vaswani et al., 2003). Fluoxetine, which antagonizes 5-HT_{2C} receptors (Carrasco & Sandner, 2005) which may in turn potentiate an agonist effect (Rajkumar & Mahesh, 2008), has also been postulated to be a 5-HT_{2A} antagonist (Rajkumar & Mahesh, 2008), (Siever, 2008). Regarding clozapine, the evidence of an antisuicidal effect in schizophrenia of this antiserotonergic antipsychotic may result from its effect as a potent 5-HT_{2A} antagonist (Schmidt et al., 1995).

More recent clinical studies suggest that lithium's antisuicidal effects relate to decreased impulsive and aggressive behavior mediated by serotonergic enhancement (Tondo & Baldessarini, 2009). In these studies, anti-impulsive and anti-aggressive effects of lithium are stated to be reflected in a reduction in the lethality of suicide attempts, based on the ratio between the number of attempts and the number of suicides registered (A/S). This ratio, which is higher in the general population (18:1) than in untreated patients with MAD (2.44:1) (Baldessarini et al., 2001), has been estimated to be increased about 2.5-fold by the effect of long-term treatment with lithium (Baldessarini et al., 2003), (Baldessarini et al., 2006).

Figure 1:

A proposed pathophysiological model of the antisuicidal effect of lithium (Adapted from (Mann, 2003) and (Siever, 2008)):

A proposed pathophysiological model of the antisuicidal effect of lithium is presented, adapted from Mann's model of the neurobiology of suicidal behavior (Mann, 2003) and Siever's model of the neurobiology of aggression and violence (Siever, 2008).

Impulsivity and aggression are contemplated in this model as major factors in suicidal behavior, putatively caused by low serotonergic function and a dysfunction of the inverse relationship between the prefrontal cortical and amygdalar activity in the regulation of emotions, aggression and impulsivity.

Neurobiological underpinnings of impulsive aggression in Siever's model are insufficient serotonergic facilitation of "top-down" regulation by prefrontal and anterior cingulated cortices of an excessive "bottom-up drive" to aggressive action, originating from hyperactivity of the amygdala and other limbic regions.

Three general mechanisms of action have been proposed for the antisuicidal effect of lithium (represented with dotted arrows): incidental to mood stabilizing, potentiation of 5-HT in the forebrain, and nonspecific factors (clinical monitoring and interpersonal factors inherent to lithium treatment).

Lithium may reinforce the "top-down" regulation by prefrontal and anterior cingulated cortices and reduce amygdalar and limbic hyperactivity (Terao, 2008).

Valproate and gabapentine may reduce amygdalar and limbic hyperactivity (Terao, 2008).

The role of clozapine, fluoxetine and paroxetine is described in the text. (ACG: anterior cingulate cortex; Li: long term lithium treatment; OFC: orbital frontal cortex; MDE: Major depressive episode; VPA: Valproate).

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e) Nonspecific factors: medical monitoring, and interpersonal / psychosocial factors inherent to lithium treatment

Maintenance care (Mann et al., 2005), with close monitoring of both psychiatric and somatic aspects (Nilsson, 1995), has potential for prevention of suicide. The quality of the doctor-patient relationship inherent to lithium treatment, which usually requires more frequent clinical follow-ups than does treatment with antidepressants and other mood stabilizers may be an important contributor to its antisuicidal effects. This enables the physician to detect the prodromal affective symptoms (Kallner et al., 2000) or psychosocial stressors that may trigger suicidal behavior, and thus enact preventive therapeutic strategies. Moreover, it provides the patient with more frequent physician contact. Indeed, an ecological study has found an association between some indicators of access to clinical care (e.g. the per-capita ratio of psychiatrists and physicians in the population) with suicide rates in the US (Tondo et al., 2006). While it has been pointed out that this additional clinical supervision may not be a critical factor (Tondo & Baldessarini, 2009), it may at least contribute to the antisuicidal effect of lithium treatment, as a variety of time-limited outpatient programs have shown efficacy targeting patients at high risk of suicide (Rudd et al., 1996) (including specific psychotherapeutic approaches (Linehan et al., 2006) , (Slee et al., 2008)).

There are also the issues around confounding by indication (doctors are afraid to give suicidal patients lithium, often viewed as a potential lethal weapon) and the fact that blood level monitor permits precise determination of effective dose as well as identification of non-adherence to treatment.

Derived clinical recommendations

Some basic general recommendations could be drawn from the studies reviewed, to be considered in two different clinical scenarios: a) the initiation of prophylactic treatment in patients with BPD and b) the affective relapses in patients with MAD already receiving

continuation treatment with lithium, in which a switching or augmentation strategy is planned.

Evidence for lithium's antisuicidal effect, together with its mood-stabilizing properties and low cost may be solid arguments for considering this drug a first choice in the prophylactic treatment of BPD (Coryell, 2009; Schou, 1999), (Cipriani et al., 2005), (Baldessarini & Tondo, 2009).

Regarding the second scenario, two considerations should be weighed. First, given that the antisuicidal effect of lithium seems to be independent of its mood-stabilizing properties, then lithium may confer protection against suicidal behavior even in patients whose mood response is inadequate. In this situation, considering also that lower suicide risk have been reported under treatment with lithium than with other mood-stabilizers (for example carbamazepine (Thies-Flechner et al., 1996) and valproate (Goodwin et al., 2003)), administration of a second mood-stabilizer in addition to lithium has been recommended in lieu of a switching strategy (Müller-Oerlinghausen, 2001), particularly for those with previous suicide attempts (Müller-Oerlinghausen et al., 1992). This consideration is in agreement with the latest results on relapse prevention in BPD from the BALANCE 2-year randomized trial, in which lithium monotherapy or a lithium and valproate combination appeared to be modestly more effective than valproate monotherapy. This study suggests that patients with relapses on lithium could be switched to lithium plus valproate, instead of valproate alone, as is currently suggested by clinical guidelines (Geddes et al., 2010).

Second, given evidence of increased suicide risk associated with lithium discontinuation, in cases of intolerance or toxicity a lithium withdrawal should be carried out with caution (Ahrens & Müller-Oerlinghausen, 2001), adopting a gradual (15–30 days) discontinuation rate (Baldessarini & Tondo, 1998) (Baldessarini et al., 1999).

To conclude, the studies reviewed herein provide evidence of plausible neurobiological underpinnings of the antisuicidal effect of lithium revealed in observational clinical reports, RCTs and

meta-analyses of RCTs. Further studies are required for a deeper elucidation of both the neurobiological basis and the clinical degree of protection against suicide provided by long-term treatment with lithium. In order to test the antisuicidal effects of lithium, randomized controlled trials are required and several have been recently published (Lauterbach et al., 2008) or are underway.

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