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CASE REPORT

Lithium Augmentation in Reboxetine-Refractory Depression

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Abstract

A substantial part of patients with major depressive episode do not respond to antidepressants. Lithium can presently be considered the best validated augmentation strategy for patients not responding to tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI's), venlafaxine, and mirtazapine. We present a report of successful lithium augmentation in a patient not responding to the highly selective noradrenaline reuptake inhibitor reboxetine. Whereas synergistic serotonergic mechanisms have habitually been proposed as the neurobiological basis of lithium augmentation, the presented observation raises the question of other possible rationalizations. Lithium augmentation should be considered as a treatment strategy in case of non response to specific noradrenergic antidepressants, and this strategy merits further investigations (German J Psychiatry 2005; 9: 31-32).

Keywords: Reboxetine, lithium, refractory depression, antidepressant drug, noradrenaline, serotonine

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Introduction

More than one third of patients with a major depressive episode in general do not respond to antidepressants (Bauer et al., 2002). Lithium can presently be considered the best validated augmentation strategy for patients not responding to tricyclic antidepressant (TCA), selective serotonin reuptake inhibitors (SSRIs)(Bschor et al., 2003; Heit and Nemeroff, 1998; Zullino and Baumann, 2001), venlafaxine (Bertschy et al., 2003; Zullino et al., 2001) and mirtazapine (Bruijn et al., 1998).

The main current hypothesis postulates a synergistic serotonergic effect of antidepressants and lithium. Lithium has been found to enhance serotonergic function among others by modulation of serotonin turnover and release (de Montigny, 1994; Price et al., 1990). Furthermore, it has been suggested to act on $5HT_{1A}$ receptors previously sensitized by the antidepressant treatment (Chaput et al., 1991; de Montigny, 1994; Heit and Nemeroff, 1998).

We present what is believed to be the first report of lithium augmentation in a patient not responding to the highly selective noradrenaline reuptake inhibitor reboxetine (Wong et al., 2000).

Case report

Mr. A, 40 years old, Caucasian, consulted because of a first major depressive episode. After a 12-weeks trial with fluoxetine up to 60mg, which had to be discontinued due to distressing anorgasmia, medication was switched to reboxetine, which was titrated up to 8 mg within 4 weeks. After 4 months of reboxetine treatment, the patient continued to present significant depressive symptoms (MADRS score of 33), complaining about depressive mood, inner tension, concentration difficulties, lassitude, reduced interests, inferiority and guilt feelings as well as suicidal thoughts. Routine laboratory and thyroid function were normal.

Lithium carbonate 900mg was added reaching 0.76mg/L after 3 days. A first notable improvement was observed

during the second week of treatment, which was corroborated by a reduction of the MADRS score to 6. No subjective or objective side effects were recorded.

During the three month follow-up, treatment remained unchanged, resulting in sustained improvement (MADRS 10). Besides the treatment changes, no life events contributing to the positive evolution could be found.

Discussion

We report what is believed to be the first successful treatment of lithium augmentation in a patient previously not responding to reboxetine. We observed significant improvements from the beginning of the second week of treatment on, analogous to observations made before for serotonergic antidepressants (Zullino and Baumann, 2001). Whereas a spontaneous remission or a placebo effect cannot be completely ruled out, the time course and the absence of any contributing life event support the augmenting effect of lithium.

Whereas synergistic serotonergic mechanisms have habitually been proposed as the neurobiological basis of lithium augmentation, our observation raises the question of other possible rationalizations. One could hypothesize a noradrenergic-serotonergic synergy, an unleashing of an otherwise blocked noradrenergic activity, and finally a serotonin and noradrenaline independent mechanism such as acting at the level of neurotrophic factors (Manji et al., 2003). Whereas the available preclinical data support mainly the noradrenaline-serotonin-interaction hypothesis, this has to be considered provisional. For example, coadministration of reboxetine and lithium in rats leads to increased concentrations of extra cellular serotonin in the medial prefrontal cortex compared to reboxetine alone (Kitaichi et al., 2004;Manji et al., 2003). Furthermore, it has been shown that the serotonin release in raphe neurons is modulated by noradrenaline (Pudovkina et al., 2002).

In conclusion, lithium augmentation should also be considered as a treatment strategy in case of nonresponse to specific noradrenergic antidepressants, and this strategy merits further investigations.

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