Botulinum toxin (BoNT) for depression:
A review of the mechanism of action and its potential place as an adjuvant treatment

BY CLARE AMRANI

BoNT is becoming a recognised efficient treatment for depression, endorsed by several disciplines including psychiatry. **Clare Amrani** examines the potential mechanism of action and explores the appropriate place of BoNT in the therapeutic armamentarium for depression.

How did BoNT become a therapeutic alternative in the field of depression?

Depression remains a very debilitating condition with a significant impact on all aspects of the patient's life and on society. Diagnosis and treatment are complex, requiring proper psychological assessment by a trained and qualified medical practitioner [1]. The main therapeutic approaches for depression remain psychotherapy and pharmacotherapy [1]. Although these mainstream conventional therapies are well-established, they are not always efficient. Conventional drugs used for depression can have significant drawbacks and their side-effects are known to lead some patients to discontinue their medication. Additionally, they can sometimes take a long time to show a positive effect on depression; and 30-50% of the patients fail to respond [2]. They are also known to create debilitating dependance in some instances [3]. For all these reasons, alternative therapies have been considered, such as magnetic stimulation, electroconvulsive therapy and ketamine, the long-term effect of the latter is still debated and controversial [4]. The use of BoNT for depression stems from a random observation, rather than a treatment developed by design [5]. Its positive effects on depression were a 'side product' first observed following glabella injection for a purely cosmetic purpose [5]. Another retrospective observational study [6], as well as randomised trials, have subsequently attempted to confirm the efficacy and establish the mechanism of action [7,8].

"A large body of evidence strongly support the effects of BoNT as a treatment for depression"

Why was the initial evidence supporting BoNT for depression mixed?

Over a period of 10 years, the majority of the studies have confirmed a significant positive effect of BoNT on depression when injected in the glabella region [9]. Other authors have only demonstrated marginal benefits with no significant difference when compared to placebo effect, even though this study was industry sponsored and led [7]. This drawback has prompted some authors to analyse the result more closely [10].

The very first explanation behind the beneficial effect of BoNT on depression was the face-brain feedback hypothesis. According to this theory, by paralysing the muscle responsible for negative emotions, the so called 'grief' muscles, namely the corrugator supercilli and procerus, this inhibits the appearance and expression of negative feelings such as sadness and anger [11]. This negative information is no longer sent to the brain [12]. Some authors [12] have gone as far as making the negative facial features (contraction of glabella) a full part of depression rather than a cause. This would imply that BoNT would act on a component of depression rather than a causal part.

Although the face to brain feedback theory has been adopted by many and has an elegant and almost logical aspect, it does bring a serious methodological issue. The positive effects of BoNT on depression were exclusively drawn from patients who had an injection in the glabella region, i.e in the muscle expressing negative emotion. With that arises the logical and pertinent question related to differential effect of placebo / nocebo effect following the purely cosmetic outcome [10]. In other words, it is legitimate to wonder whether the positive effect on depression is the by-product of the satisfaction that the cosmetic results generate.

This is further complicated by the fact that other authors found that patients who did not have static glabella lines present or were not concerned about their lines, also had a positive effect from BoNT on depression [13]. This would support the notion that the BoNT effect on depression seems to work on its own, i.e independently from any inhibition of the face-brain feedback.

Is the face-brain feedback viable as a sole theory?

In order to answer this question and clarify the mechanism of action, a large meta-analysis has taken the logical steps to examine whether the effect of BoNT in depression was observed in patients who had BoNT for a non-glabella injection [10]. The purpose of this meta-analysis was to eliminate the potential role of the placebo / nocebo on depression, by looking at patient outcomes in a non-cosmetic setting [24-26]. These authors reached the conclusion that BoNT works equally well on depression in a non-cosmetic setting [10]. Therefore, the face-brain feedback theory as a sole mechanism of BoNT on depression can no longer hold on its own.

Although this is the most widely referred to theory, there is no definite neurophysiological or anatomical substrate to it. However, some experimental studies have attempted to elucidate it [12,14,15]. In a rodent model using validated

experimental features mimicking clinical symptoms of depression, as well as biological markers for depression, some authors have demonstrated that symptoms of depression were reduced following peripheral BoNT injection. They also demonstrated that BoNT injection has the ability to increase the level of noradrenaline, 5-hydroxytryptamine (5-HT) and various other markers known to be reduced in depression [14]. Although this experimental study showed a clear correlation between peripheral BoNT injection and improvement of depression-like symptoms, as well as markers of depression, it does not explain the neurological pathway through which this effect is exerted. A potential theory is the retrograde axonal pathway (movement) of BoNT towards the brain [16].

A more clinical orientated study, using magnetic resonance imaging (MRI) to assess the amygdala activity following BoNT injection has corroborated the face to brain feedback theory [17]. Although small in design, this study has demonstrated that following the paralysis of the so called 'grief' muscles, the activity within the portion of the brain responsible for negative emotion, namely the amygdala is reduced. Even more interesting was the fact that the MRI activity returned to the baseline once the BoNT effect subsided. This study seems to suggest a central neurological substrate for the so-called face to brain feedback theory. However, like other studies it does not give any explanation as to how this feedback is transported to the brain.

What is the other alternative mechanism of BoNT on depression?

Although not fully demonstrated, the positive effect of BoNT injected peripherally improved depression via the central nervous system. This concept is now adopted and supported by several authors [9,14,17]. Another study has shown that the level of acetylcholine is higher than normal in patients suffering from depression [18]. It would be tempting to extrapolate that BoNT induced the reduction of acetylcholine within the brain. This could be considered as an important pathway in the treatment of depression.

Stimulation of the cerebral limbic region as a result of the 'grief' muscles contraction is further evidence supporting the central nervous system as a support for the facial feedback phenomenon [12,19]. The mechanism through which cerebral acetylcholine is reduced as a result of peripheral injection of BoNT remains elusive.

Other studies support a non-central pathway. These authors imply that the classic effects of BoNT on peripheral nerves act on the brain by influencing the messages sent by the afferent neurological pathways [20]. This theory is again based on speculation and has no neurophysiological evidence to support it.

Other potential mechanisms of action are variations of the face-brain feedback theory and relate to the positive effect of cosmetic results on demonstrable parameters such as increased self-confidence, a better quality of life, improvement of self-perception and simply satisfaction [13]. The most intriguing aspect of this study was that a particular patient who had a negative perception of cosmetic changes has had a significant improvement of his depression symptoms. Although this is an anecdotal report in one patient, if confirmed, it would suggest that the effect of BoNT on depression is independent from any notion of grief muscle inhibition.

Several psychosocial studies have emphasised the role of social feedback. This theory is also a variation of the face to brain theory and refers to the notion that the inhibition of the facial negative expression by BoNT directly influences the reaction of the close social circle towards the patient. This in return will have a positive action on self-awareness. In other words, people with a negative facial expression tend to experience a negative social attitude towards them [21,22]. The inhibition of this negative facial expression would trigger a reverse social effect, namely a positive social attitude towards the patient [21,22]. This theory is contradicted by another study that reported patients who received BoNT injections reported a neutral attitude at best, and a clear rejection at worst [23].

All the available research put together strongly supports the beneficial effect of BoNT on depression. Even the field of psychiatry has now endorsed BoNT as a potential therapeutic option for depression [9]. Paradoxically, this treatment has been adopted without an exact and unanimously accepted mechanism. Although backed by several studies, all the above-mentioned mechanisms and theories are largely speculative. Currently available robust basic science experimental studies [14] as well as dynamic imaging studies [17] very strongly support the notion that the face to brain feedback has a neurological platform. Others have even demonstrated that a particular facial emotion or expression correlates to a specific brain site [15]. Nonetheless, there is so far no evidence to show any anatomical substrate (i.e. afferent system) between the face and the brain.

The effect of BoNT on pain is well established and pain relief with all the beneficial effects on wellbeing [16,24] might also be an explanation for the effect of BoNT on depression which seems to occur regardless of the site of injection [10,25].

Conclusion

Given the large body of evidence supporting the efficacy of BoNT on depression, it has become a potential additional treatment to the already large therapeutic armamentarium. Further research needs to be undertaken to determine its exact place and who should be carrying out these specialised treatments. Given the fact that depression is a very complex condition, this treatment should only be carried out in conjunction with and under the supervision of specialised teams in mental health [1].

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