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 EDITORIAL
 

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## Botulinum toxin and spasticity

The clinical effects of botulinum toxin have been recognised since the end of the 19th century. It is the most potent neurotoxin known and it is produced by the gram negative anaerobic bacterium *Clostridium botulinum*. The paralytic effect of the toxin is due to blockade of neuromuscular transmission.<sup>1</sup> Injection into a muscle causes chemodeneration and local paralysis and this effect has led to the development of the toxin as a therapeutic tool. It is now used clinically for a wide range of conditions,<sup>2</sup> particularly focal dystonias, and increasingly for spasticity. This paper reviews the mode of action of botulinum and focuses on its use in the management of spasticity.

### Clinical pharmacology

There are seven immunologically distinct serotypes of botulinum toxin (labelled A–G). This review concentrates on the only type in routine clinical use—type A (BTX-A). Currently, type B,<sup>3</sup> type C,<sup>5</sup> and type F<sup>6–8</sup> are being investigated for clinical use and type B may be available in the near future.

Botulinum toxin acts at the neuromuscular junction by inhibiting the release of acetylcholine. It acts selectively on peripheral cholinergic nerve endings causing chemical denervation after the binding, internalisation, and activation of the toxin at the neuromuscular junction. The toxin is synthesised as a relatively inactive single polypeptide chain.

Selective high affinity binding of BTX-A occurs at the neuromuscular junction. After internalisation, it is activated when its structure is modified by cleavage of the disulfide bond linking the light and heavy chain. The N terminal of the heavy chain then promotes penetration and translocation of the light chain across the endosomal membrane into the cytosol. This then interacts with, and cleaves the fusion protein SNAP 25 (synaptosomal associated protein) inhibiting the calcium mediated release of acetylcholine from the presynaptic nerve terminal.<sup>9</sup> Nerve sprouting and muscle re-innervation lead to functional recovery within 2 to 4 months.

Type E acts in the same way, types B, D, F and G act similarly, but cleave the vesicular associated membrane protein (VAMP) and type C acts by cleaving syntaxin and SNAP 25.

Botulinum toxin type A is commercially purified for clinical use and marketed as Dysport® (Ipsen) and BOTOX® (Allergan). A vial of Dysport® contains 500 Units and a vial of BOTOX® contains 100 Units. There

are significant differences between the potencies of these products in the clinical situation and an equivalency ratio of Dysport®/BOTOX® ranging from 3:1 to 4:1 is generally accepted.<sup>11–13</sup>

### Subtypes of botulinum toxin

Other serotypes of botulinum toxin may have a future part to play—particularly in those who fail to respond to BTX-A.

Studies have shown that type B is effective, safe, and well tolerated with mild and transient side effects.<sup>3</sup> Type B seems to be effective in both A responders and A non-responders.<sup>14</sup> Its adverse event profile is similar to type A. Antibodies to type A do not cross react with type B; therefore this toxin has considerable potential for use in those failing to respond to BTX-A, or as an alternative first line treatment.

The temporal profile and effects of type C are similar to type A<sup>5</sup> and type F is also effective in A resistant patients with neutralising antibodies. However, its mean duration of 5 weeks is shorter than that of BTX-A, thus limiting its clinical usefulness.<sup>7</sup> <sup>15</sup> <sup>16</sup>

### Clinical issues

Despite botulinum toxin being a potent neurotoxin, the safety profile of its purified form is impressive.<sup>17</sup> However, there are some side effects and a few contraindications. The latter include myasthenia gravis, Lambert-Eaton syndrome, and other neuromuscular disorders, pregnancy, and the use of aminoglycoside antibiotics.

### SIDE EFFECTS

These can be either local or systemic. The most common local adverse effect is weakness. This is usually minimal and transient and occurs because of local diffusion of the toxin.<sup>18</sup> <sup>19</sup> Dysphagia, for example, can occur after injections for the treatment of cervical dystonia.<sup>20</sup> <sup>21</sup> Ptosis is the most common problem after injections for blepharospasm and hemifacial spasm.<sup>22</sup> <sup>23</sup>

Systemic adverse effects, although rare, include transient flu-like symptoms, anaphylaxis, and excessive fatigue. Cases of generalised muscular weakness have been reported<sup>24</sup> <sup>25</sup> and abnormal neuromuscular transmission (albeit subclinical) has been demonstrated using single fibre EMG<sup>26</sup> in muscles distant from the site of injection.

### IMMUNORESISTANCE

Most people injected with the toxin continue to show responsiveness at repeated treatments. However, some do

not respond initially (primary non-responders) and others respond initially but fail to respond with subsequent injections (secondary non-responders). Antibody production is thought to be the cause of this secondary non-response.

In the clinical situation, antibody resistance should be suspected in those who show secondary non-responsiveness, no response, or a poor clinical response to BTX-A injections. Clinical guidelines for the evaluation of secondary non-responsiveness have recently been published.<sup>27</sup> If immunoresistance is suspected, the eyebrow and frontalis tests are useful<sup>28</sup> or an antibody assay such as the *in vivo* mouse protection bioassay, or preferably a radioimmunoprecipitation assay<sup>29</sup> could be carried out. However, in practical terms the injections are usually continued until the clinical response becomes insignificant. At this time other treatment options should be considered. Anecdotally some patients seem to respond to substitution of the alternative manufacturer's type A toxin. Other people seem to benefit from a botulinum "holiday" of about 6 months. After this break some patients will once again respond. However, there is no published evidence confirming the efficacy of these two approaches. Hopefully in the near future type B toxin will be available and should be helpful in the management of type A non-responders.

Factors which may affect the risk of developing immunoresistance include the dosage used and the time interval between injections. Higher amounts seem more likely to lead to antibody production.<sup>30</sup> To reduce the likelihood of non-responsiveness, using the lowest dose to achieve the desired effect is suggested.<sup>31 32</sup> The likelihood of antibody production also increases with shorter dosage intervals.<sup>14 17 31</sup>

### Therapeutic uses

Botulinum toxin type A is currently used for various conditions.<sup>32</sup> The table indicates some of the commoner conditions reported in the literature, with appropriate supporting references. The current licensed indications for Dysport® and BOTOX® are blepharospasm, hemifacial spasm, cervical dystonia, and the treatment of dynamic equinus foot deformity in people with cerebral palsy, from 2 years old. Its use in spasticity is the focus of this article.

#### SPASTICITY

Spasticity can lead to significant physical problems including spasms, restricted range of movement, pain, and contractures, as well as functional difficulties including the

#### Reported uses of botulinum toxin

Diagnosis	References
Strabismus	(33)(34)
Blepharospasm*	(35) (22) (36) (37)(38)
Oromandibular dystonia	(36) (39)
Hemifacial spasm*	(22) (40) (23)
Task specific dystonia	(41)
Laryngeal dystonia	(42)(43)
Cervical dystonia*	(20)(21) (36)(37) (44)(45)(46)(47)(48)
Acquired nystagmus	(49)
Oscillopsia	(34)
Tremor	(50)(51)(52)(53)(54)
Tics	(2)
Detrusor sphincter dyssynergia	(55)(56)(57)(58)
Achalasia	(59)
Anismus/vaginismus	(60)
Cosmesis	(61)
Hyperhidrosis	(62)(63)(64)
Myofascial pain	(65)
Temporomandibular joint dysfunction	(2)
Cervicogenic headache	(66)
Spasticity*	See text

Licensed uses denoted by\*.

maintenance of personal hygiene. Treatment is usually aimed at improving function, alleviating pain, or minimising complications. Regimes focus on physiotherapy, including appropriate seating and orthoses, oral medications, phenol, or alcohol nerve blocks and the use of more advanced techniques such as intrathecal baclofen and surgery.<sup>67</sup> However, spasticity, particularly after focal brain lesions, will tend to be focal in nature. Thus, systemic medication is often inappropriate and treatment needs to concentrate on the relevant overactive muscle groups—hence the potential value of botulinum.

#### GENERAL USE

The first report in 1989<sup>68</sup> confirmed the efficacy and safety of BTX-A in spasticity and several open labelled and other studies went on to support these findings.<sup>69-77</sup> Thus, the early work with BTX-A in spasticity from varying aetiologies was positive. The treatment seemed safe with the potential both to reduce spasticity and improve function. Further studies then focused on spasticity secondary to specific causes and began to provide more precise data about appropriate techniques, dosages, and the use of adjunctive therapy.

#### Stroke

Early open label studies investigated the use of BTX-A in people with upper limb spasticity secondary to stroke and all supported its use and provided evidence of its effectiveness in reducing muscle tone.<sup>72 75 76</sup>

Hesse and Mauritz<sup>72</sup> found the use of higher dosages (1600 MU Dysport®) injected into a greater number of sites, using EMG guidance, to be most effective in reducing spasticity. If the spasticity was reduced, ease of personal care was reported to increase although changes on disability rating scales were not achieved. Bhakta *et al*<sup>75</sup> suggested that BTX-A is safe and effective at reducing both disability and spasticity in those with severe upper limb spasticity. By contrast, others<sup>76</sup> confirmed improvements in spasticity but found that most people studied rated their functional improvement as none or mild. However, only hand and finger flexors were injected—leaving elbow flexors untreated and thus resulting in little improvement in disability. A multicentre randomised, double blind, placebo controlled trial studied the use of the toxin in poststroke severe upper extremity spasticity.<sup>78</sup> Thirty nine patients (all at least 9 months after stroke and thus at a stage when natural improvement was unlikely) were randomised to receive either placebo or one of three different doses of BOTOX® (75, 150, or 300 units) into the elbow and wrist flexors. Treatment with the highest dose resulted in a statistically significant mean decrease in muscle tone for up to 6 weeks after injection but there were no significant differences between placebo and treatment for motor functions, pain, caregiver dependency, and competence in daily activities. However, this result was not in accord with results obtained in other open series<sup>75 79</sup> that had shown an increased range of motion, facilitation of hand hygiene, and improved motor function. The lack of demonstrable functional benefit in this study may be because most of the cases had reasonable function at baseline, with little scope for improvement and the global functional measures used may not have been sufficiently sensitive. The standardised injection criteria also meant that other involved muscles could not be treated appropriately. Hence it seems that BTX-A treatment needs to be individualised, particularly for muscles injected. Rigid protocols are inappropriate.

Other studies<sup>80 81</sup> have confirmed efficacy and safety in lower limb spasticity. Significant positive changes on the

Ashworth scale<sup>80</sup> and on gait analysis variables<sup>81</sup> have been found, as well as subjective improvements.

#### *Multiple sclerosis and traumatic brain injury*

In multiple sclerosis the beneficial effect of BTX-A on focal spastic muscle contractions was shown in a double blind, cross over trial involving nine people with chronic multiple sclerosis.<sup>82</sup> Injection into the adductor muscle group resulted in statistically significant reductions in spasticity and improvements in ease of nursing care. Other uncontrolled reports supported these findings.<sup>73 74 77 83</sup>

Only a few reports specifically consider spasticity secondary to traumatic brain injury. In one open labelled study, 21 people with severe spasticity in the wrist and finger flexors were injected with BOTOX®,<sup>84</sup> Passive range of movement exercises and casting were also employed as clinically indicated. Statistically significant improvements in range of movement and spasticity were documented in both the acutely (up to 12 months) and chronically (more than 12 months) injured. The effect of botulinum toxin on tone in the early stages of rehabilitation has also been evaluated.<sup>85</sup> The upper limb muscles found to be contributing to the spasticity on clinical examination were injected under EMG guidance in six people with severe traumatic brain injury. Although improvements in activities of daily living were described and statistically significant improvements on the Ashworth scale and range of movements occurred, the results may have been confounded by the use of casting. Another case study<sup>86</sup> also showed a significant reduction in tone with the use of toxin in lumbrical spasticity—an important disability.

#### *Cerebral palsy*

Spasticity is a major problem in cerebral palsy. Animal model work supported the theory that tone reduction in the spastic muscle, using BTX-A, reverses the failure of longitudinal muscle growth.<sup>87</sup> If this is translated into the child then BTX-A has the potential to correct motor imbalance, improve functional position and gait, and delay or obviate the need for surgery.

Several open studies reported the beneficial effects of BTX-A when used in cerebral palsy for the treatment of both upper and lower limb spasticity.<sup>88-90</sup> Cosgrove *et al*<sup>88</sup> injected 26 children, both ambulatory and non-ambulatory, who had dynamic contractures of the lower limb interfering with positioning or walking. A reduction in tone occurred within 3 days of the injections and lasted from 2 to 4 months. In addition, a subjective functional improvement was also noted by the parents and ambulatory status improved. The total dosage used was from 100–400 MU Dysport® per child and no side effects were noted. In a similar population, Koman *et al*<sup>89</sup> injected the paraspinal and lower limb muscles, demonstrating a decrease in tone and improvement in positioning and gait. Others<sup>90</sup> have looked at injections into the adductor pollicis for the treatment of the thumb in palm deformities. Although splinting was also used, all cases showed improvements in cosmesis and function.

The first double blind placebo controlled trial included 12 children with dynamic equinovarus deformities.<sup>91</sup> Significant improvements in muscle tone and motor performance were demonstrated in the treatment group after injections into the medial and lateral heads of the gastrocnemius muscle. There were no side effects with the dosage of 2 MU/kg body weight.

Others have used 4 MU/kg BOTOX®.<sup>92</sup> This was injected into the gastrocnemius muscle as a treatment for equinus gait in 26 cases. Significant improvements in the gait analysis variables of dynamic ankle dorsiflexion in both

swing and stance phases, stride length, and EMG of the tibialis anterior were obtained.

Others<sup>93 94</sup> not only describe a reduction in tone but also comment on a reduction in pain, increased ease of care, and increased function. One group<sup>95</sup> reported the use of BTX-A in both spastic and dystonic cerebral palsy in children as young as 1 year old. They indicated that some of their most successful results were in children under the age of 3. Most authors propose early treatment, preferably before 6 years, in an effort to avoid the development of fixed contractures.

Another randomised double blind placebo controlled trial has studied the effects of BTX-A injections in the upper limb.<sup>96</sup> In 14 children with a dynamic component to their spasticity, BOTOX® was used at a dose of 4 MU/kg (90–250 MU) and Dysport® was used at a dose of 8–9 MU/kg (160–400 MU). Significant increases in maximum active elbow and thumb extension and significant decreases in wrist and elbow tone were obtained in combination with a modest functional change. A notable point was the cosmetic benefit found from the reduction in involuntary elbow flexion.

More recently trials have compared the use of the toxin with more conservative forms of treatment such as casting.<sup>97</sup> In 20 children with dynamic calf equinus, the efficacy of BTX-A and casting were similar using three dimensional video gait analysis and clinical examination as the short term outcome measures. However, the tone reduction in the toxin group allowed a more prolonged improvement in passive dorsiflexion, which could potentially allow more opportunity for an increase in muscle length.

On the whole, the use of toxin in cerebral palsy is effective but careful goal planning and objective assessments should be used.

#### ADJUNCTIVE THERAPY

Botulinum is rarely a treatment in isolation. In clinical practice it is often combined with ongoing physiotherapy, orthoses, and perhaps continuing oral medication. A few studies have evaluated the efficacy of BTX-A in combination with other treatment modalities.<sup>98 99</sup> Hesse *et al*<sup>98</sup> compared the effects of a combination of selective, lower dose BTX-A injections (100 MU BOTOX®) into the tibialis posterior with ankle taping compared with toxin alone into calf muscles. Both groups showed a reduction in spasticity, increased gait velocity, and step length and a change in the position of the foot, at rest and during passive movement. Although the conclusion was that both regimes were effective in reducing foot inversion, the combination group had less gain in passive dorsiflexion. These findings supported previous suggestions that higher dosages of BTX-A are more effective at correcting foot position and increasing the passive range of movements.<sup>70 74 81</sup> However, the specific problem of inversion can be satisfactorily treated using a combined approach and this may represent a more cost effective solution<sup>79</sup> and may also reduce the risk of antibody development.<sup>100</sup>

A randomised placebo controlled study assessed combination treatment with short term electrical stimulation<sup>99</sup> using four treatment groups in 24 people with stroke. Injections of either placebo or toxin (1000 MU Dysport®) into six upper limb flexor muscles were combined with additional electrical stimulation in two of the groups. The stimulation was given three times for half an hour for 3 days and assessments occurred before and after injection. Most improvements were seen in the combination group with a statistically significant improvement in palm cleaning, differences in tone, and placing the arm through a sleeve. This may indicate that short term electrical stimulation

enhances the effectiveness of BTX-A. Further studies are now needed to determine the place of botulinum toxin in combination with other treatments.

### Conclusions

The usefulness of BTX-A in the management of various clinical conditions is increasing. Its use for the treatment of some movement disorders is now well accepted.<sup>32</sup>

It is increasingly being used for the management of focal spasticity secondary to various aetiologies in adults, and in childhood cerebral palsy. It is suggested that functional benefits may be enhanced by careful patient selection and individualised treatment. Its reversible yet long lasting action, ease of administration, and favourable safety and adverse effect profile are factors that contribute to its usefulness. However, the optimal time to initiate treatment and the potential for combination treatment needs more research. There are two major limitations. Firstly, the cost of the toxin is appreciable and more widespread usage and increasing indications will begin to have a significant impact on purchasers of health services. Secondly, the need for repeat injections means that attendees in botulinum clinics will steadily increase. The introduction of trained nurse practitioners to administer injections in those with stable requirements may be a way around this logistic problem.<sup>101</sup>

Overall, botulinum toxin has been a major advance in the field of movement disorders and in the management of spasticity.

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## EDITORIAL COMMENTARIES

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# Acoustic neuroma surgery as an interdisciplinary approach

For such a relatively rare tumour, acoustic neuroma continues to hold a remarkable fascination for both neurosurgeons and neuro-otologists. The Third International Conference on Acoustic Neuroma in Rome last June continued for 5 days!

The early controversies in the management of acoustic neuromas were largely about the surgical approaches which might be used and about the outcome of facial nerve function. In this period the improved outcomes which could be achieved by utilising the combined expertise of otologists and neurosurgeons, were clearly demonstrated. Likewise, the advantages to be gained by monitoring facial nerve function were also firmly established. More recently, controversy has shifted to the question of hearing preservation and, in particular, to the unresolved problem of what constitutes “useful” hearing. The place of intraoperative brain stem auditory evoked response (BAER) audiometry in improving hearing outcomes is still uncertain, largely because of the known difficulties in

obtaining reliable recordings. However, on empirical grounds it is likely that if hearing preservation rates are to improve, BAER audiometry will play a significant part in this improvement. The paper<sup>1</sup> by Tonn *et al* in this issue (pp 161–166) once more emphasises the benefits of interdisciplinary teamworking. It also indicates that BAER monitoring may indeed have a part to play in improved hearing outcomes. However, it also raises other perhaps more interesting questions. The series is large and the analysis of the patient material indicates that 78.5% of the series had “good” hearing preoperatively (grade 1–3 on the Gardner-Robertson scale). This is a remarkably high proportion of patients with “good” preoperative hearing. In the Cambridge series (now 725 patients) the number of patients who have “good” preoperative hearing are in a substantial minority. Most of our patients have had either “dead” ears or very poor hearing. This is a significant difference and I suspect that it reflects the unsatisfactory level of delay inherent in current United Kingdom

practice for the management of acoustic neuromas. In this country, when patients first become aware that something may be wrong, they go in the first instance to their general practitioners, then, often after a substantial wait, are referred to and eventually seen by an ear, nose, and throat surgeon. By the time the necessary investigations have been performed, the various results assembled, and an appointment made further time has elapsed. Referral onwards to the "acoustic team" may involve significant further delay. When a decision to operate has eventually been made, a further period of delay on a waiting list may then occur. By the time the patient eventually comes to surgery the hearing has not infrequently by then deteriorated to the level at which any efforts directed to its preservation are usually pointless. This is clearly very unsatisfactory. In Germany, as in most developed countries elsewhere, they do things differently and such delays are not inherent in their systems. The system we have adopted in the United Kingdom is often euphemistically described as "gatekeeping" but in fact acts as a covert form of "rationing" and is clearly to the detriment of our patients. If in the United Kingdom we are to improve our rate of hearing preservation, a first step must be to treat the continuing risk to hearing as a matter of some urgency. It must be better for our patients if we are able to eliminate the various delays between initial presentation and surgery. Wherever possible we should be able to intervene while acceptable levels of hearing are still present.

The controversy about how to measure "acceptable" hearing continues. The use of the term "good" or "useful" hearing is no longer acceptable and, if used in scientific papers, a clear definition of what is meant by the term should also be set out. In our paper,<sup>2</sup> the difficulties of comparative assessment of hearing results are set out. It is now, I think, generally accepted that concepts, such as "serviceable hearing" or "good functional hearing" are insufficiently accurate to serve as useful comparators for results. It is generally agreed among British otologists and neurosurgeons that a less than 30 dB loss on pure tone audiogram and a speech discrimination score of 70% or

more represents the best definition of "good", "serviceable", "good functional" or "socially useful" hearing and I would make a plea for this definition to be accepted as the gold standard for these terms. If such criteria are used then the number of cases with "good" or "socially acceptable" preoperative hearing is likely to be much fewer than reported in most recent series and the postoperative outcomes will be correspondingly somewhat worse. Unless preoperative and postoperative hearing results are reported in this objective manner comparison of hearing outcomes becomes very difficult. All papers which do not report their results in this manner should now perhaps carry a "government health warning".

In our series, under these strict criteria, our postoperative hearing preservation rate is poor (less than 5%). The only preoperative factor that predicted a favourable hearing preservation outcome was the presence of normal preoperative BAER morphology. The outcomes in the paper by Tonn *et al* seem substantially better but direct comparisons are not possible as audiological and speech discrimination results are not explicitly given. However, it may nevertheless be correct that our hearing preservation results are indeed poorer than those of our more progressive neighbours. In surgery great technical breakthroughs are rare: the usual method of progress is by incremental improvements applied to a multiplicity of separate factors but it is much easier to identify those factors which might count if we have clear and comparable reporting criteria beforehand. It is also true that we should not first shoot ourselves in the foot by accepting such long delays before embarking on our surgery so that the exercise has already become pointless.

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## Cerebral dysfunction and psychotic symptoms in Alzheimer's disease

Psychotic phenomena are far from uncommon in Alzheimer's disease; delusions are present in up to three quarters of patients, hallucinations in up to a half. They appear as the disease progresses into its middle phase and are associated with cognitive decline. A better understanding of the psychopathogenetic mechanisms through which psychotic experience is mediated would have implications that would extend well beyond Alzheimer's disease; in this respect it could provide a neurological model for the so called functional psychoses. Some studies have used functional neuroimaging to identify those parts of the brain implicated in the psychotic process. The findings have been inconsistent. The paper by Mega *et al* in this issue (pp 167-171)<sup>1</sup> describes a methodology that represents a distinct advance. The neuropsychiatric inventory<sup>2</sup>, a caregiver based instrument, was employed to control for concomitant behaviours other than those that are psychotically driven. Ten behavioural variables were rated, only

two of which, delusions and hallucinations, are psychotic. A close match was achieved for non-psychotic behaviours as well as for sex, cognitive performance, and education, but only at a cost: the initial pool of 210 patients was reduced to psychotic and non-psychotic groups of 10 patients each.

The groups so formed underwent single photon emission computed tomography (SPECT) neuroimaging. In the psychotic group perfusion was significantly lower in 11 regions, most of which were clustered in the prefrontal cortex bilaterally, the left striatum, and the left parietal cortex. Reductions in regional perfusion in the temporoparietal cortex are characteristic of Alzheimer's disease<sup>3</sup>: reductions in prefrontal cortical perfusion would not necessarily have been predicted, so inevitably these findings provoke speculation concerning the role of executive function (or rather dysfunction) in the appearance of psychotic phenomena. These are not necessarily generated in the

prefrontal striatal areas (for example, there is some evidence to implicate the middle temporal cortex in the production of hallucinations<sup>4</sup>) but Mega *et al* are right to emphasise the critical significance of executive failure: a psychotic hallucination is not simply an isolated perceptual aberration; it owes its distinctive psychotic quality to the failure of insight, influential judgement, and self monitoring capacity that are characteristic of executive dysfunction.

Psychotic symptoms are not usually present during the early stages of Alzheimer's disease. Does their emergence signify the advance of Alzheimer's pathology into the prefrontal regions? Future studies that seek to replicate these

findings should include measures of executive function in their study design.

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